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Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

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## UTILITY PATENT APPLICATION

EPI-067191 Attorney Docket No. First Inventor or Application Identifier Jonathan W. Nyce LOW ADENOSINE ANTI-SENSE OLIGONUCLEOTIDE... TRANSMITTAL

(Only for new nonprovisional app loations under 37 C.F.R. § 1.53(b))

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	APPLICATION ELEMENTS hapter 600 concerning utility patent application contents.	Assistant Commissioner for Patents  ADDRESS TO:  Box Patent Application  Washington, DC, 20231
1. <b>V</b> (S	Fee Transmittal Form (e.g., PTO/SB/17) Submit an original and a duplicate for fee processing)	5. Microfiche Computer Program (Appendix)
2. 🗸 S <sub>I</sub>	pecification [Total Pages ]	Nucleotide and/or Amino Acid Sequence Submission     (if applicable, all necessary)
	preferred arrangement set forth below)  Descriptive title o the Invention	a. Computer Readable Copy
- (	Cross Reference: to Related Applications	b. Paper Copy (identical to computer copy)
1	Statement Regarding Fed sponsored R & D	
_	Reference to Microfiche Appendix Background of the Invention	c. Statement verifying identity of above copies
	-	ACCOMPANYING APPLICATION PARTS
	Brief Summary of the Invention  Brief Description of the Drawings ( <i>if filed)</i>	7. Assignment Papers (cover sheet & document(s))
	Detailed Description	37 C.F.R.§3.73(b) Statement Power of
- (	Claim(s)	(when there is an assignee) Attorney (2)  9. English Translation Document (if anning the)
	Abstract of the Disclosure	Information Displacture
3 Dr	rawing(s) (35 U.S.C. 113) [Total Sheets ]	10. Statement (IDS)/PTO-1449 Copies of IDS Citations
4. Oath or l	Declaration [Total Pages ]	11. Preliminary Amendment
a.	Newly executed (original or copy)	12. Return Receipt Postcard (MPEP 503) (Should be specifically itemized)
b.	Copy from a prior application (37 C.F.R. § 1.63( (for continua ion/divisional with Box 16 completed)	d)) * Cmoll Ensite
_	j. DEI ETION OF INVENTOR(S)	13. Statement(s) Statement filed in prior application (PTO/SB/09-12) Status still proper and desired
	Signed statement attached deleting	Certified Copy of Priority Document(s)
	inveritor(s) named in the prior application see (17 C.F.R. §§ 1.63(d)(2) and 1.33(b).	(if foreign priority is claimed)
* NOTE FOR	ITEMS 1 & 13: IN ORDER TO BE ENTITY FO TO PAY SMALL ENTITY	Toller.
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16. If a CO	NTINUING APPI.ICATION, check appropriate box, and s	upply the requisite information below and in a preliminary amendment.
	ontinuation Divisional Continuation-in-part (C	P) of prior application No: 60,127958
For CONTINU	plication information: Examiner	Group / Art Unit:  If the prior application, from which an oath or declaration is supplied
under box 40	i, is considered a part of the disclosure of the accompanyl	a gentination or divisional application and is hereby incorporated by as been inadvertently omitted from the submitted application parts.
	17. CORRESPONDE	
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### IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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For:

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LOW ADENOSINE ANTI-SENSE OLIGONUCLEOTIDE, COMPOSITIONS,

KIT & METHOD FOR TREATMENT OF AIRWAY DISORDERS

ASSOCIATED WITH BRONCHOCONTRICTION, LUNCH

INFLAMMATION, ALLERGY(IES) & SURFACTANT DEPLETION

#### **COVER LETTER**

**Box: New Application** 

Assistant Commissioner of Patents & Trademarks Washington, DC 20231

Sir\Madam:

Enclosed for filing are the following:

- 1. Utility Patent Application Transmittal Form
- 2. Fee Transmittal Form
- 3. Assignments (2) and Recordation form and \$40.00
- 4. U.S. Non-Provisional Paten Application
- 5. Sequence Listing, Declaration and diskette
- 6. IDS & 1449-PTO Form Listing References
- 7. Declarations (2)
- 8. Small Entity Status form
- 9. Postcard

Respectfully submitted. ARTER & HADDEN

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I hereby certify that this paper or fee is being deposited with the United States Postal Service via Express Mail service in an Express Mail Package under label No. EJ664079305US under 37 CFR 1.8 on the date indicated above and is addressed to the Assistant Commissioner for Patents, Washington D C 20231, prApril 4, 2000, by Jenny R. Wilson

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#### LOW ADENOSINE ANTI-SENSE OLIGONUCLEOTIDE, COMPOSITIONS, KIT & METHOD FOR TREATMENT OF AIRWAY DISORDERS ASSOCIATED WITH BRONCHOCONSTRICTION, LUNG INFLAMMATION, **ALLERGY(IES) & SURFACTANT DEPLETION**

#### **BACKGROUND OF THE INVENTION**

#### Field of the Invention

This patent relates to a composition comprising oligonucleotides (oligos) that are anti-sense to adenosine receptors, and contain low amounts of or no adenosine (A). These agents are suitable for the treatment, among others, of pulmonary diseases associated with inflammation, impaired airways, including lung disease and diseases whose secondary effects afflict the lungs of a subject. Examples of these diseases are allergies, asthma, impeded respiration, allergic rhynitis, pain, cystic fibrosis, and cancers such as leukemias, e.g. colon cancer, and the like. The present agent may be administered prophylactically or therapeutically in conjunction with other therapies, or may be utilized as a substitute for therapies that have significant, negative side effects.

#### 15 Background of the invention

Respiratory ailments, associated with a variety of diseases and conditions, are extremely common in the general population, and more so in certain ethnic groups, such as African Americans. In some cases they are accompanied by inflammation, which aggravates the condition of the lungs. Asthma, for example, is one of the most common diseases in industrialized countries. In the United States it accounts for about 1% of all health care costs. An alarming increase in both the prevalence and mortality of asthma over the past decade has been reported, and asthma is predicted to be the preeminent occupational lung disease in the next decade. While the increasing mortality of asthma in industrialized countries could be attributable to the depletion reliance upon beta agonists in the treatment of this disease, the underlying causes of asthma remain poorly understood.

Adenosine may constitute an important mediator in the lung for various diseases, including bronchial asthma. Its potential role was suggested by the finding that asthmatics respond favorably to aerosolized adenosine with marked bronchoconstriction whereas normal individuals do not. An asthmatic rabbit animal model, the dust mite allergic rabbit model for human asthma, responded in a similar fashion to aerosolized adenosine with marked bronchoconstriction whereas non-asthmatic rabbits showed no response. More recent work with this animal model suggested that adenosine-induced bronchoconstriction and bronchial hype responsiveness in asthma may be mediated primarily through the stimulation of adenosine receptors. Adenosine has also been shown to cause adverse effects, including death, when administered therapeutically for other diseases and conditions in subjects with previously undiagnosed hyper reactive airways.

A handful of medicaments have been available for the treatment of respiratory diseases and conditions, although in general they all have limitations. Theophylline, an important drug in the treatment of asthma, is a known adenosine receptor antagonist which was reported to eliminate adenosine-mediated bronchoconstriction in asthmatic rabbits. A selective adenosine A<sub>1</sub> receptor antagonist, 8-cyclopentyl-1, 3dipropylxanthine (CPCPX) was also reported to inhibit adenosine-mediated bronchoconstriction and bronchial hyperresponsiveness in allergic rabbits. The therapeutic and preventative applications of currently available adenosine A<sub>1</sub> receptor-specific antagonists are, nevertheless, limited by their toxicity. Theophylline, for example, has been widely used in the treatment of asthma, but is associated with frequent, significant toxicity resulting from its narrow therapeutic dose range. DPCPX is far too toxic to be useful clinically. The fact that, despite decades of extensive research, no specific adenosine receptor antagonist is available for clinical use attests to the general toxicity of these agents. Anti-sense oligonucleotides have received considerable theoretical consideration as potential useful pharmacological agents in human disease. Their practical application in actual models of human disease, however, has been somewhat elusive. Cne important impediment to their effective application has been a difficulty in finding

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an appropriate route of administration to deliver them to their site of action. Many in vivo experiments were conducted by administering anti-sense oligonucleotides directly to specific regions of the brain. These applications, however, necessarily have limited clinical utility due to their invasive nature. Although antisense oligonucleoticles have received considerable theoretical consideration for their potential use as pharmacological agents in human disease, finding practical and effective applications for these agents in actual models of hur an disease, however, have been few and far between, particularly because they had to be administered in large doses. Another important consideration in the pharmacologic application of these molecules is their route of administration. Many in vivo applications have involved the direct administration of anti-sense oligonucleotides to limited regions of the brain. Such applications, however, have limited clinical utility due to their invasive nature. The systemic administration of anti-sense oligonucleotides as pharmacological agents has been found to have also significant problems, not the least of which being an inherent difficulty in targeting disease-involved tissues. That is, the necessary dilution of the anti-sense oligonucleotide in the circulatory system makes extremely difficult to attain a therapeutic dose at the target tissue by intravenous or oral administration. The bioavailability of orally administered anti-sense oligonucleotides is very low, of the order of less than about 5%. Anti-sense oligonucleotides have been used in therapy by many, including the present inventor, who in his previous work successfully treated various diseases and conditions by direct administration of these agents to the lung. In many instances, other workers have had to face the difficulties associated with the delivery of DNA molecules to a desired target. Thus, the route of administration may be of extreme importance for treating generalized diseases and conditions as well as those which are localized. In contrast, up to the present time, the delivery of anti-sense agents to the lung has been relatively undeveloped. As described by the present inventor in more detail below, the lung is an excellent target for the direct administration of anti-sense oligonucleotides

Clearly, there exist presently no effective therapies for treating these ailments, or at least no therapies which are effective and devoid of significant detrimental side effects. Accordingly, there is still a need for an agent for the treatment of adenosine mediated ailments afflicting the pulmonary and respiratory ailments affecting the lung airways, including respiratory problems, bronchoconstriction, inflammation, allergy(ies), depletion or hyposecretion of surfactant, etc., which is highly effective and sufficiently selective to avoid detrimental side effects produced by other therapies. In addition, there is a definite need for making available a delivery method that will require low amounts of therapeutic agents and will be effective for the rap d and targeted access of tissue genes of mRNAs and the reversal of untoward effects afflicting a subject.

and provides a non-invasive and a tissue-specific route.

#### SUMMARY OF THE INVENTION

The present invention generally relates to a pharmaceutical or veterinary composition, comprising an anti-sense oligonucleotide(s) (oligo(s)) which is (are) effective for alleviating bronchoconstriction and/or lung inflar mation, allergy(ies), and/or surfactant depletion and/or hyposecretion, when administered to a mammal, the oligo containing about 0 to about 15% adenosine (A) and being anti-sense to a target selected from the group consisting of the initiation codon, the coding region, the 5'-end and the 3'-end genomic flanking regions, the 5' and 3' intron-exon junctions, and regions within 2 to 10 nucleotides of the junctions of a gene encoding a target polypeptide associated with lung airway dysfunction or antisense to the polyreptide mRNA; combinations of the oligos; and mixtures of the oligos; and a pharmaceutically or veterinarily acceptable carrier or diluent. The targets are typically molecules associated with airway disease, cancer, etc., such as transcription factors, stimulating and activating peptide factors, cytokines, cytokine receptors, chemokines, chemokine receptors, adenosine receptors, bradykinin receptors, endogenously produced specific and non-specific enzymes, immunoglobulins and antibodies, antibody receptors, central nervous system (CNS) and peripheral nervous and non-nervous system receptors, CNS and peripheral nervous and non-nervous system peptide transmitters, adhesion molecules, defensins, growth factors, vasoactive peptides and receptors, binding proteins, and malignancy associated proteins, among others. Examples are oligo(s) targeted to adenosine receptor(s) and it(they) are typically

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present in the composition in an amount effective to reduce adenosine mediated effect(s), such as airway obstruction, inflammation, allergy(ies), and sufactant depletion, among others. The adenosine receptor is preferably selected from the group consisting of the adenosine A<sub>1</sub>, A<sub>26</sub>, and A<sub>3</sub> receptors, and in some instances even adenosine A<sub>2a</sub> receptors. The oligo of the invention may be applied to the preparation of a medicament for (a) reducing adenosine-mediated bronchoconstriction, impeded respiration, inflammation, allergy(ies), depletion production of surfactant, and other detrimental pulmonary effects in a subject in need of treatment, and/or for (b) treating specific diseases and conditions such as asthma, cystic fibrosis, allergic rhynitis, COPD, etc. For the first time this invention provides the targeted administration of one or more oligonucleotides directly into the repiratory system. The oligos may be directed to any target and are intended for fast delivery through the mucosal tissue of the lungs for hybridization to a desired target polynucleotide, e. g. mRNA, to prevent gene transcription and translation, such that protein expression will be reduced, hampered, or completely stopped. Thus, this invention also provides a more general method for administering oligonucleotides that are anti-sense to targeted genes and mRNAs associated with any type of diseases, by lirect administration into the respiratory system, e. g. by inhalation, by introduction of a solution or aerosol into the respiratory airways, and/or directly into the lung.

The present oligos, moreover, are suitable for reducing effects mediated by a variety of target proteins and genes, for example adenosine-mediated effects, including pulmonary, respiratory, and other associated effects, e. g. bronchoconstriction, inflammation, immune mediated reactions, allergy(ies) and other airway problems, which may be caused by different conditions, including cancer. Examples of diseases and conditions, which may be treated preventatively, prophylactically and therapeutically with the agent of this invention, are pulmonary vasoconstriction, inflammation, allergies, asthma, impeded respiration, respiratory distress syndrome, pain, cystic fibrosis, allergic rhynitis, pulmonary hypertension, pulmonary vasoconstriction, emphysema, chronic obstructive pulmonary disease (COPD), bronchitis, and cancers such as leulemias, lymphomas, carcinomas, and the like, e.g. colon cancer, breast cancer, lung cancer, pancreatic cancer, hepatocellular carcinoma, kidney cancer, melanoma, hepatic metastases, etc., as well as all types of cancers which may metastasize or have metastasized to the lung(s), including breast and prostate cancer. The present agents are also suitable for administration before, during and after other treatments, including radiation, chemotherapy, antibody therapy, phototherapy and cancer, and other types of surgery. The present agent is effectively administered prophylactically and therapeutically in conjunction with other therapies, or by itself for conditions without known therapies or as a substitute for therapies that have significant negative side effects. The oligo(s) may be administered by any means known to a subject, e. g. to the lungs of the subject, more generally through any and all systemic and topical routes. This oligonucleotide(s) (oligo(s)) employed are anti-sense to to a target DNA or RNA, e. g. an adenosine receptor DNA or RNA, and preferably consist essentially of up to about 15% adenosine (A), and more preferably contain no adenosine. The oligos are provided in the form of specific compositions and formulations, with a carrier or diluent, and optionally with other therapeutic agents and additives which are used for administration by specific routes, e.g. into the respiratory system, topically, transdermally, parenterally, by implantation, and the like. The oligo is also provided as a capsule or cartridge, and in the form of a kit. The oligos of the invention may be produced by selection of specific targeted segments of the gene or mRNA incoding the adenosine receptor as described below. In one preferred embodiment, the selection is made to obtain oligos that consisting essentially of less than about 15% adenosine (A). This may be done by selecting the target as done above, which includes genes, genomic flanking regions, RNAs and polypeptide associated with an ailment afflicting the lung airways, obtaining the sequence of a mRNA(s) correspording to the target gene(s) and/or their genomic flanking region(s) and/or the juxtamembrane regions thereof, and mRNA(s) encoding the target polypeptide(s), selecting at least one segment of the mRNA(s), and synthesizing one or more anti-sense oligonucleotide(s) to the selected mRNA segment(s), and substituting, if necessary, an alternative, e. g. a universal base(s) or other base(s) for one or more A to reduce the proportion of A present in the oligonucleotide to less than about 15%, and down to no adenosine. Similarly, alternative and/or universal bases may be substituted for adenosine, e. g. specific

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adenosine A1, A2b and A3 receptor antagonists or A2a receptor agonists, theophilline, enprophylline, and many other adenosine receptor antagonists known in the art as well as agonists with significantly reduced agonist activity with respect to adenosine, e. g. less than 0.5%, less than 0.3%, and the like.

The invent on will now be described in general in conceptual and experimental terms, with reference to specific examples. Other objects, advantages and features of the present invention will become apparent to those skilled in the art from the description that follows.

#### **DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS**

This invention arose from a desire by the inventor to improve on prior art treatments for pulmonary and othe diseases, which technology is generally frought with detrimental side effects and by the need of administering high doses of therapeutical agents. The present invention arises from the inventor's own discovery that adenosine receptor targeted anti-sense oligonucleotides (oligos) may be utilized therapeutically in the treatment of diseases or conditions which impair respiration, cause inflammation and/or allergy(ies), constrict bronchial tissue, obstruct the lung airways, depletion surfactant secretion, or otherwise impede normal breathing. In general, many diseases and conditions are associated with or cause inflam nation, constrict bronchial tissue or the lung airways, depletion secretion of surfactant, augment allergy(ies), or otherwise impede normal breathing. This treatment is selective for specific targets associated with or mediating these symptoms, and the agents are administered in up to 1000-fold lower doses than those seen in the art. The inventor, in addition, wanted to provide a treatment which would improve the outcome and life style of patients undergoing other procedures or being administered other therapies, including antibody therapy, chemotherapy, radiation, phototherapy, and surgery e.g. cancer surgery, and that could be effectively administered preventatively, prophylactically or therapeutically. He reasoned that he could further improve on this discovery by selecting oligos of reduced adenosine content, or reducing the ade iosine content of otherwise targeted anti-sense oligos corresponding to endogenous polynucleotide sequences. The present invention is premised on the discovery by the inventor that oligonucleotides are metabolized in vivo to their mononucleotides. Adenosine (A)-containing oligonucleotides break down and release adenosine which, in turn, activates adenosine receptors, thereby causing bronchoconstriction, inflammation, surfactant depletion, allergy(ies), and the like. He, thus, conceived of employing low adenosine-free adenosine oligos to avoid these side effects upon their administration. He succeeded in this endeavor and is providing in this patent novel and improved compositions, formulations and methods which afford greatly improved results when compared with previously known treatments for preventing and alleviating bronchoconstriction, allergy(ies), inflammation, breathing difficulties, surfactant depletion and blockage of airways, as well as for other conditions which affect the lung directly or indirectly. In different embodiments, one or more nucleic acids of the invention may be formulated alone, and/or with one or more surfactant components and/or with a carrier, and/or with other therapeutic agents and/or formulation agents known in the art. The compositions of this invention, thus, may be incorporated into a variety of formulations for systemic and topical administration. Moreover, the inventor also provides a broad method for delivery of anti-sense oligonucleotides (ol gos) through the respiratory system, as a fast means of starting treatment to address acute attacks of asthma and other diseases and conditions that have a rapid onset. In addition, the present agents have long ha flives and may be administered at very low doses. This makes them ideal for once a In the past, anti-sense oligonucleotides received considerable theoretical week type therapies. consideration as being potentially useful as pharmacologic agents for the treatment of human disease. Wagner, R., Nature 372: 333-335 (1994). However, it has been difficult to actually apply these molecules to alleviating and curing human diseases. One important consideration in the pharmacologic application of these molecules has been the failure of various routes of administration to deliver the compounds to its target while avoiding invading the circulation and, therefore, other untargeted tissues which, thus, produces a plethora of side effects. Most in vivo experiments utilizing anti-sense oligonucleotides involved a direct application of the ol go to limited regions of the brain. See, Wahlestedt, C., Trends in Pharmacol. Sci. 15: 42-46 (1994); Lai, .. et al., Neuroreport 5: 1049-1052 (1994); Standifer, K., et al., Neuron 12: 805-810

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(1994); Akabayashi, A., et al., Brain Res. 21: 55-61 (1994). Others applied them into the spinal fluid. See, e.g. Tseng, L., et al., European J. Pharmacol. 258: R1-3 (1994); Raffa, R., et al., European J. Pharmacol. 258: R5-7 (1994); Gillardon, F., et al., European J. Neurosci. 6: 880-884 (1994). Such applications, clearly, have no practical clinical utility due to their invasive nature. Thus, the systemic administration of anti-sense oligonucleotides poses significant problems with respect to their pharmacologic application, not the least of which is the difficulty in selectively targeting disease-involved tissues. The systemic administration of anti-sense oligonucleotides also poses significant problems with respect to their pharmacologic application, not the least of which is the difficulty in selectively targeting disease-involved tissues.

The respira ory system, and in particular the lung, as the ultimate port of entry into the organism, however, is an excellent route of administration for anti-sense oligonucleotides. This is so not only for the treatment of lung disease, but also when utilizing the lung as a means for delivery, particularly because of its non-invasive and tissue-specific nature. Thus, local delivery of antisense oligonucleotides directly to the target tissue enables the therapeutic use of these compounds. Fomivirsen (ISIS 2302) is an example of a local drug delivery into the eye to treat cytomegalovirus (CMV) retinitis, for which a new drug application has been filed by ISIS. The administration of a drug through the lung offers the further advantage that inhalation is non-invasive whereas direct injection in to the vitreous of the eye is invasive. The composition and formulations of this invention are highly efficacious for preventing and treating diseases and conditions associated with bronchoconstriction, difficult breathing, impeded and obstructed lung airways, allergy(ies), inflammation and surfactant depletion, among others. Examples of diseases and conditions which are suitably treated by the present method are diseases and conditions, including Acute Respiratory Distress Syndrome (ARDS), asthma, adenosine administration e.g. in the treatment of SupraVentricular Tachycardia (SVT) and other arrhythmias, and in stress tests to hyper-sensitized individuals, ischemia, renal damage or failure induced by certain drugs, infantile respiratory distress syndrome, pain, cystic fibrosis, pulmonary hypertension, pulmonary vasoconstriction, emphysema, chronic obstructive pulmonary disease (COPD), lung transplantation rejection, pulmonary infections, and cancers such as leukemias, lymphomas, carcinomas, and the like, including colon cancer, breast cancer, lung cancer, pancreatic cancer, hepatocellular carcinoma, kidney cancer, melanoma, hepatic metastases, etc., as well as all types of cancers which may metastasize or have metastasized to the lung(s), including breast and prostate cancer. The invention will be described with respect to the adenosine receptors as targets, but is similarly applicable to any other target with respect to the pulmonary administration of anti-sense oligos. The examples provided below show a complete inhibition of such adenosine receptor associated symptoms in a rabbit model for human bronchoconstriction, allergy(ies) and inflammation as well as the elimination of the ability of the adenosine receptor agonist par excellence, adenosine, to cause bronchoconstriction in hyper-responsive monkeys, which are animal models for human hyper-responsiveness to adenosine receptor agonists. The pharmaceutical composition and formulations of the invention, therefore, are suitable for preventing and alleviating the symptoms associated with stimulation of adenosine receptors, such as the adenosine  $A_1$  receptors. The compositions and formulations of this invention, thus, are also suitable for preven the untoward side effects of adenosine-mediated hyperresponsiveness in certain individuals, which are generally seen in diseases affecting respiratory activity.

The method of the present invention may be used to treat airway diseases and conditions in a subject of any kind and for any reason, with the intention that the adenosine content of anti-sense compounds be minimized, reduced or eliminated so as to prevent its liberation upon anti-sense degradation. Examples of diseases and conditions, which may be treated preventatively, prophylactically and therapeutically with the compositions and formulations of this invention, are pulmonary vasoconstriction, inflammation, allergies, asthma, allergic rhynitis, impeded respiration, Acute Respiratory Distress Syndrome (ARDS), renal damage and failure associated with ischemia as well as the administration of certain drugs, side effects associated with adenosine administration e.g. in SupraVentricular Tachycardia (SVT) and in adenosine stress tests, infantile Respiratory Distress Syndrome (infantile RDS), ARDS, pain,

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cystic fibrosis, pulrionary hypertension, pulmonary vasoconstriction, emphysema, chronic obstructive pulmonary disease (COPD), lung transplantation rjejection, pulmonary infections, and cancers such as leukemias, lymphor as, carcinomas, and the like, e.g. colon cancer, breast cancer, lung cancer, pancreatic cancer, hepatocellular carcinoma, kidney cancer, melanoma, metastatic cancer such as hepatic metastases, lung, breast and prostate metastases, among others. The present compositions and formulations are suitable for administration before, during and after other treatments, including radiation, chemotherapy, antibody therapy, phototherapy and cancer, and other types of surgery. The present compositions and formulations may also be administered effectively as a substitute for therapies that have significant negative side effects. The terms "anti-sense" oligonucleotides generally refers to small, synthetic oligonucleotides, resembling single-stranded DNA, which in this patent are applied to the inhibition of gene expression by inhibition of a targe messenger RNA (mRNA). See, Milligan, J. F. et al., J. Med. Chem. 36(14), 1923-1937 (1993), the relevant portion of which is hereby incorporated in its entirety by reference. For consistency=s sake, all RNAs and oligonucleotides are represented in this patent by a single strand in the 5' to 3' direction, when read from left to right, although their complementary sequence(s) is (are) also encompassed within the four corners of the invention. In addition, all nucleotide bases and amino acids are represented utilizing the recommendations of the IUPAC-IUB Biochemical Nomenclature Commission, or by the known 3-letter code (for amino acids). Nucleotide sequences are presented herein by single strand only, in the 5' to 3' direction, from left to right. In addition, nucleotide and amino acids are represented herein in the manne recommended by the IUPAC-IUB Biochemical Nomenclature Commission, or (for amino acids) by three letter code, in accordance with 37 CFR ' 1.822 and established usage. See, e.g., PatentIn User Manual, 99-102 (Nov. 1990) (U.S. Patent and Trademark Office, Office of the Assistant Commissioner for Patents, Washington, D.C. 20231); U.S. Patent No. 4,871,670 to Hudson et al. at col. 3, lines 20-43. The present method utilizes anti-sense agents to inhibit or down-regulate gene expression of target genes, including those listed in Tables 1 and 2 below. This is generally attained by hybridization of the anti-sense oligonucleotides to coding (sense) sequences of a targeted messenger RNA (mRNA), as is known in the art. The exogenously administered agents of the invention decrease the levels of mRNA and protein encoded by the target gene and/or cause changes in the growth characteristics or shapes of the thus treated cells. See, M lligan et al. (1993); Helene, C. and Toulme, J. Biochim. Biophys. Acta 1049, 99-125 (1990); Cohen, J. S. D., Ed., Oligodeoxynucleotides as Anti-sense Inhibitors of Gene Expression; CRC Press: Boca Raton, FL (1987), the relevant portion of which is hereby incorporated in its entirety by reference. As used herein, "anti-sense oligonucleotide or asnti-sense oligo" is generally a short sequence of synthetic nucleotide that (1) hybridizes to any segment of a mRNA encoding a targeted protein under appropriate hybridization conditions, and which (2) upon hybridization causes a decrease in gene expression of the targeted protein. The terms "desAdenosine" (desA) and "des-thymidine" (desT) refer to oligonucleotides substantially lacking either adenosine (desA) or thymidine (desT). In some instances, the des A or des T sequences are naturally occurring, and in others they may result from substitution of an undesirable nucleotide (A) by another lacking its undesirable activity, such as acting as an agonist or having a triggering e fect at the adenosine A receptor(s). In the present context, the substitution is generally accomplished by substitution of A with a "universal or alternative base", presently known in the art or to be ascertained at a later time. As used herein, the terms "prevent", "preventing", "treat" or "treating" refer to a preventative, prophylactic, maintenance, or therapeutic treatment which decreases the likelihood that the subject administered such treatment will manifest symptoms associated with adenosine receptor stimulation. The term "down-regulate" refers to inducing a decrease in production, secretion or availability and, thus, a decrease in concentration, of intracellular target product, be it a receptor e. g. adenosine A<sub>1</sub>, A<sub>2b</sub>, A<sub>3</sub>, bradykinin 2B, GATA-3, or other receptors, or an increase in concentration of the adenosine A<sub>2a</sub> receptor. The present technology relies on the design of anti-sense oligos targeted to mRNAs associated with ailments involving lung airway pathology(ies), and on their modification to reduce the occurrence of undesirable side effects caused by their release of adenosine upon breakdown, while preserving their activity and efficacy for their intended purpose. In this manner, the inventor targets a specific gene to

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design one or more anti-sense oligonucleotide(s) (oligos) that selectively bind(s) to the corresponding mRNA, and then reduces, if necessary, their content of adenosine via substitution with an alternative or a universal base, or an adenosine analog incapable of significantly, or having substantially reduced ability for, activating or antagonizing adenosine  $A_1$ ,  $A_{2b}$  or  $A_3$  receptors or which may act as an agonist at the adenosine  $A_{2a}$ , receptor. Any number of adenosines present may be substituted by an alternative and/or universal base, such as heteroaromatic bases, which binds to a thymidine base but has less than about 0.3 of the adenosine base agonist or antagonist activity at the adenosine  $A_1$ ,  $A_{2a}$ ,  $A_{2b}$  and  $A_3$  receptors. Based on his prior experience in the field, the inventor reasoned that in addition to "downregulating" specific genes, he could increase the effect of the agent(s) administered by either selecting segments of RNA that are devoid, or have a low content, of thymidine (T) or, alternatively, substitute one or more adenosine(s) present in the designed oligonucleotide(s) with other nucleotide bases, so called universal bases, which bind to thymidine but lack the ability to activate adenosine receptors and otherwise exercise the constricting effect of adenosine in the lungs, etc. Given that adenosine (A) is a nucleotide base complementary to thymidine (T), when a T appears in the RNA, the anti-sense oligo will have an A at the same position.

In one aspect of this invention, the anti-sense oligonucleotide has a sequence which specifically binds to a portion or segment of a mRNA molecule which encodes a protein associated with impeded breathing, allergy(ies), lung inflammation, depletion of lung surfactant or lowering of lung surfactant, airway obstruction, bronchitis, and the like. One effect of this binding is to reduce or even prevent the translation of the co responding mRNA and, thereby, reduce the available amount of target protein in the subject=s lung. In one preferred embodiment of this invention, the phosphodiester residues of the antisense oligonucleotide are modified or substituted. Chemical analogs of oligonucleotides with modified or substituted phosphodiester residues, e.g., to the methylphosphonate, the phosphotriester, the phosphorothioate, the phosphorodithioate, or the phosphoramidate,  $\alpha$ = methoxy ethyl and similar modifications, which increase the in vivo stability of the oligonucleotide are particularly preferred. The naturally occurring phosphodiester linkages of oligonucleotides are susceptible to some degree of degradation by cellular nucleases. Many of the residues proposed herein, on the contrary, are highly resistant to nuclease degradation. See, Milligan et al.; Cohen, J. S. D., supra. In another preferred embodiment of the invention, the oligonucleotides may be protected from degradation by adding a "3'-end cap" by which nuclease-resistant linkages are substituted for phosphodiester linkages at the 3' end of the oligonucleotide. See Tidd, D. M. and Warenius, H.M., Be. J. Cancer 60: 343-350 (1989); Shaw, J.P. et al., Nucleic Acids Res. 19: 747-750 (1991), the relevant section of which are incorporated in their entireties herein by reference. Phosphoramidates, phosphorothioates, and methylphosphonate linkages all function adequately in this manner for the purposes of this invention, as do  $\alpha$ ' modifications, such as  $\alpha$ ' methoxy ethyl, and the like. The more extensive the modification of the phosphodiester backbone the more stable the resulting agent, and in many instances the higher their RNA affinity and cellular permeation. See, Milligan, et al., supra. In addition, a plurality of substitutions to the carbohydrate ring are also known to improve stability of nucleic acids. Thus, the number of residues which may be modified or substituted will vary depending on the need, target, and route of administration, and may be from 1 to all the residues, to any number in between. Many different methods for replacing the entire phosphodiester backbone with novel linkages are known. See, Millikan et al, supra. Preferred backbone analogue residues include phosphoramidate, phosphorothioate, methylphosphonate, phosphorotriester, phosphotriester, thioformacetal, phosphorodithioate, phosphoramidate, formacetal, triformacetal, thioether, carbamate, boranophosphate, 3'-thioformacetal, 5'-thioether, carbonate, C<sub>5</sub>-substituted nucleotides, 5'-N-carbamate, sulfate, sulfonate, sulfamate, sulfonamide, sulfone, sulfite, 2'-O methyl, sulfoxide, sulfide, hydroxylamine, methylene(methylimino) (MMI). methoxymethyl (MOM), and methoxyethyl(MOE), methyleneoxy(methylimino) (MOMI) residues, and combinations thereof. Phosphorothioate methylphosphonate- nodified oligonucleotides are particularly preferred due to their availability through automated oligonuc eotide synthesis. See, Millikan et al, supra. Where appropriate, the agent of this

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invention may be administered in the form of their pharmaceutically acceptable salts, or as a mixture of the anti-sense oligonucle otide and its salt. In another embodiment of this invention, a mixture of different antisense oligonucleotides or their pharmaceutically acceptable salts is administered. A single agent of this invention has the capacity to attenuate the expression of a target mRNA and/or various agents to enhance or attenuate the activity of a pathway. By means of example, the present method may be practiced by identifying all possible deoxyribonucleotide segments which are low in thymidine (T) or deoxynucleotide segments low in a lenosine (A) of about 7 or more mononucleotides, preferably up to about 60 mononucleotides, more preferably about 10 to about 36 mononucleotides, and still more preferably about 12 to about 21 mononucleotides, in a target mRNA or a gene, respectively. This may be attained by searching for mono nucleotide segments within a target sequence which are low in, or lack thymidine (RNA), a nucleotide which is complementary to adenosine, or that are low in adenosine (gene), that are 7 or more nucleotides long. In most cases, this search typically results in about 10 to 30 such sequences, i.e. naturally lacking or having less than about 40% adenosine, anti-sense oligonucleotides of varying lengths for a typical target mRNA of average length, i.e., about 1800 nucleotides long. Those with high content of T or A, respectively, may be fixed by substitution of a universal base for one or more As. The agent(s) of this invention may be of any suitable length, including but not limited to, about 7 to about 60 nucleotides long, preferably about 12 to about 45, more preferably up to about 30 nucleotides long, and still more preferably up to about 21, although they may be of other lengths as well, depending on the particular target and the mode of delivery. The agent(s) of the invention may be directed to any and all segments of a target RNA. One preferred group of agent(s) includes those directed to an mRNA region containing a junction between an intron and an exon. Where the agent is directed to an intron/exon junction, it may either entirely overlie the junction or it may be sufficiently close to the junction to inhibit the splicing-out of the intervening exon during processing of precursor mRNA to mature mRNA, e.g. with the 3' or 5' terminus of the anti-sense oligonucleotide being positioned within about, for example, within about 2 to 10, preferably about 3 to 5, nucleo ide of the intron/exon junction. Also preferred are anti-sense oligonucleotides which overlap the initiation codon, and those near the 5' and 3' termini of the coding region. The flanking regions of the exons may also be targeted as well as the spliced segments in the precursor mRNAs. The mRNA sequences of the ade nosine receptors and of many other targets are derived from the DNA base sequence of the gene expressing either receptors, e. g. the adenosine receptors, the enzymes, factors, or other targets associated with airway disease. For example, the sequence of the genomic human A<sub>1</sub> adenosine receptor is known and is disclosed in U.S. Patent No. 5,320,963 to Stiles, G., et al. The A<sub>3</sub> adenosine receptor has been cloned, sequenced and expressed in rat (see, Zhou, F., et al., P.N.A.S. (USA) 89: 7432 (1992)) and human (see, Jacobson, M. A., et al., U.K. Patent Application No. 9304582.1 (1993)). The sequence of the adenosine A<sub>2b</sub> receptor gene is also known. See, Salvatore, C. A., Luneau, C. J., Johnson, R. G. and Jacobson, M., Geno nics (1995), the relevant portion of which is hereby incorporated in its entirety by reference. The sequences of many of the remaining exemplary target genes are also known. See, GenBank, NIH. The sequences of those genes whose sequences are not yet available may be obtained by isolating the target segments applying technology known in the art. Once the sequence of the gene, its RNA and/or the protein are known, an anti-sense oligonucleotides may be produced according to this invention as described above to reduce the production of the targeted protein in accordance with standard techniques. The sequences for the adenosine A<sub>2a</sub> bradykinin, and other genes as well as methods for preparation of oligonucleotides are also known as those of many other target genes and mRNAs for which this invention is suitable. Thus, anti-sense oligonucleotides that downregulate the production of target sequences associated with airway disease, including the adenosine A<sub>1</sub>, A<sub>2a</sub>, A<sub>2b</sub>, A<sub>3</sub>, bradykinin, GATA-3, COX-2, and many other receptors, may be produced in accordance with standard techniques. Examples of diseases and conditions which are suitably treated by the present method are diseases and conditions, including Acute Respiratory Distress Syndrome (ARDS), asthma, adenosine administration e.g. in the treatment of SupraVentricular Tachycardia (SVT) and other arrhythmias, and in stress tests to hyper-sensitized individuals, ischemia, renal damage or failure induced by certain drugs, infantile respiratory distress

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syndrome, pain, cys ic fibrosis, pulmonary hypertension, pulmonary vasoconstriction, emphysema, chronic obstructive pulmonary disease (COPD), pulmonary transplantation rejection, pulmonary infections, and cancers such as leukemias, lymphomas, carcinomas, and the like, including colon cancer, breast cancer, lung cancer, pancreatic cancer, hepatocellular carcinoma, kidney cancer, melanoma, hepatic metastases, etc., as well as all types of cancers which may metastasize or have metastasized to the lung(s), including breast and prostate cancer.

The adenosine receptors discussed above are mere examples of the high power of the inventor=s technology. In fact, a large number of genes may be targeted in a similar manner by the present agent(s), to reduce or down-regulate protein expression. By means of example, if the target disease or condition is one associated with impeded or reduced breathing, bronchoconstriction, chronic bronchitis, pulmonary bronchoconstriction and/or hypertension, chronic obstructive pulmonary disease (COPD), pulmonary transplantation rejection, pulmonary infections, allergy, asthma, cystic fibrosis, respiratory distress syndrome, cancers, which either directly or by metastasis afflict the lung, the present method may be applied to a list of potential target mRNAs, which includes the targets listed in Table 1 and Table 2 below, among others. The anti-sense agent(s) of the invention have a low A content to prevent its liberation upon in vivo degradation of the agent(s). For example, if the system is the pulmonary or respiratory system, a large number of genes is involved in different functions, including those listed in Table 1 below.

Table 1: Pulmonary Disease or Condition Pulmonary and Inflammation Targets

	Nf6B Transcription Factor	Interleukin-8 Receptor (IL-8 R)
)	Interleukin-5 Receptor (IL-5R)	Interleukin-4 Receptor (IL-4R)
	Interleukin-3 Receptor (IL-3R)	Interleukin-1β (IL-1β)
	Interleukin-1β Receptor (IL-1βR)	Eotaxin
	Tryptase	Major Basic Protein
	β2-adrenergic Receptor Kinase	Endothelin Receptor A
	Endothelin Receptor B	Preproendothelin
	Bradykinin B2 Receptor (B2BR)	IgE (High Affinity Receptor)
	Interleukin-1 (IL-1)	Interleukin 1 Receptor (IL-1 R)
	Interleukin-9 (IL-9)	Interleukin-9 Receptor (IL-9 R)
	Interleukin-11 (IL-1 )	Interleukin-11 Receptor (IL-11 R)
	T 1 11 1 3 TH. 1 O 1 1 O 1	

30 Inducible Nitric Oxide Synthase Cyclooxygenase (COX)

Intracellular Adhesic n Molecule 1 (ICAM-1) Vascular Cellular Adhesion Molecule

Substance P (VCAM)

Rantes Endothelial Leukocyte Adhesion Molecule Endothelin ETA Receptor

(ELAM-1)

Cyclooxygenase-2 (COX-2) GM-CSF, Endothelin-1 Monocyte Activating, Factor Neutrophil Chemotactic Factor

Neutrophil Elastase Defensin 1,2,3

Muscarinic Acetylcholine Receptors Platelet Activating Factor

Tumor Necrosis Factor α 5-lipoxygenase Phosphodiesterase IV Substance P Substance P Receptor Histamine Receptor

Chymase CCR-1 CC Chemokine Receptor

Interleukin-2 (IL-2) Interleukin-4 (IL-4) Interleukin-12 (IL-12) Interleukin-5 (IL-5) Interleukin-6 (IL-6) Interleukin-7 (IL-7)

Interleukin-8 (IL-8) Interleukin-12 Receptor (IL-12R)

Interleukin-7 Receptor (IL-7R) Interleukin-1 (IL-1) Interleukin-14 Receptor (IL-14R) Interleukin-14

CCR-2 CC Chemoki ne Receptor CCR-3 CC Chemokine Receptor CCR-4 CC Chemokine Receptor CCR-5 CC Chemokine Receptor Prostanoid Receptors GATA-3 Transcription Factor

Neutrophil Adherence Receptor MAP Kinase

Interleukin-15 (IL-15) Interleukin-15 Receptor (IL-15R)



Interleukin-11 (IL-11) Interleukin-11 Receptor (IL-11R)

**NFAT Transcription Factors** STAT 4 MCP-2 MIP-1α MCP-3 MCP-4

Cyclophillin (A, B, etc.) Phospholipase A2 Basic Fibroblast Growth Factor Metalloproteinase CSBP/p38 MAP Kinase Tryptase Receptor PDG2 Interleukin-3 (IL-3)

Interleukin-10 (IL-10) Cyclosporin A - Binding Protein

10 FK506-Binding Protein α4β1 Selectin Fibronectin <u>α4β7 Selectin</u>

Table 1: Pulmonary Disease or Condition Pulmonary and Inflammation Targets

cMad CAM-1 LFA-1 (CD11a/CD18) PECAM-1 LFA-1 Selectin C3bi PSGL-1 E-Selectin P-Selectin CD-34 L-Selectin

p150.95 Mac-1 (CD11b/CD18)

Fucosyl transferase VLA-4 20 STAT-1 STAT-2 CD-18/CD11a CD11b/CD18

ICAM2 and ICAM3 C5a

CCR3 (Eotaxin Receptor) CCR1, CCR2, CCR4, CCR5 LTB-4 AP-1 Transcription Factor

Protein kinase C Cysteinyl Leukotriene Receptor

Tachykinnen Receptors (tach R) I6B Kinase 1 & 2

Interleukin-2 Recept or (IL-2R) (e.g., Substance P, NK-1 & NK-3 Receptors)

STAT 6 c-mas

NF-Interleukin-6 (NF-IL-6) Interleukin-10 Receptor (IL-10R) 30 Interleukin-3 (IL-3) Interleukin-2 Receptor (IL-2R) Interleukin-13 (IL-13) Interleukin-12 Receptor (IL-12R) Interleukin-14 (IL-14) Interleukin-6 Receptor (IL-6R) Interleukin-16 (IL-16) Interleukin-13 Receptor (IL-13R) Medullasin Interleukin-16 Receptor (IL-16R)

Adenosine  $A_1$  Receptor  $(A_1 R)$ Tryptase-I

Adenosine  $A_{2b}$  Receptor  $(A_{2b} R)$ Adenosine A<sub>3</sub> Receptor (A<sub>3</sub> R)

β Tryptase STAT-3

Adenosine A<sub>2a</sub> Receptor (A<sub>2a</sub> R) IgE Receptor  $\beta$  Subunit (IgE R  $\beta$ ) Fc-epsilon receptor CD23 antigen IgE Receptor α Subunit (IgE R α)

IgE Receptor Fc Epsilon Receptor (IgERFc ξ R) Substance P Receptor

Histidine decarboxylase Tryptase-1

Prostaglandin D Syn:hase Eosinophil Cationic Protein Eosinophil Derived Neurotoxin Eosinophil Peroxidase

Endothelial Nitric Oxide Synthase Endothelial Monocyte Activating Factor

45 Neutrophil Oxidase Factor Cathepsin G

Macrophage Inflamr atory Protein-1-Interleukin-8 Receptor α Subunit (IL-8 Rα)

Alpha/Rantes Receptor Endothelin Receptor ET-B

These genes, and others, are involved in the normal functioning of respiration as well as in diseases associated vith respiratory pathologies, including cystic fibrosis, asthma, pulmonary hypertension and vasoconstriction, chronic obstructive pulmonary disease (COPD), pulmonary transplantation rejection, pulmonary infections, chronic bronchitis, respiratory distress syndrome (ARDS), allergic rhinitis, lung cancer and lung metastatic cancers and other airway diseases, including those with inflammatory response.

Anti-sense oligos to the target receptors, e. g. the adenosine A<sub>1</sub>, A<sub>2a</sub>, A<sub>2b</sub>, and A<sub>3</sub> receptors, CCR3 (chemokine receptors), bradykinin 2B, CAM (vascular cell adhesion molecule), and eosinophil receptors,

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among others, have been shown to be effective in down-regulating the expression of their genes. Some of these act to alleviate the symptoms or reduce respiratory ailments and/or inflammation, for example, by "down regulation" of the adenosine A1, A2a, A2b, and/or A3 receptors and CCR3, bradykinin 2B, VCAM (vascular cell adhesion molecule) and eosinophil receptors. These agents may be utilized by the present method alone or in conjunction with anti-sense oligos targeted to other genes to validate pathway and/or networks in which they are involved. For better results, the oligos are preferably administered directly into the respiratory system, e.g., by inhalation or other means, of the experimental animal, so that they may reach the lungs without widespread systemic dissemination. This permits the use of low agent doses as compared with those administered systemically or by other generalized routes and, consequently, reduces the number and degree of undesirable side effects resulting from the agent=s widespread distribution in the body. The agent(s) of this invention has (have) been shown to reduce the amount of receptor protein expressed by the tissue. These agents, thus, rather than merely interacting with their targets, e.g. a receptor, lower the number of target proteins that other drugs may interact with. In this manner, the present agent(s) afford(s) extremely high efficacy with low toxicity. Anti-sense oligonucleotides to the A<sub>1</sub>, A<sub>2b</sub>, A<sub>3</sub>, bradykinin B2, GATA-3, CAM (vascular cell adhesion molecule), eosinophil receptors, and COX-2 receptors, among others, have been shown to be effective in the down-regulation of the respective receptor proteins in the cell. One novel feature of this treatment, as compared to traditional treatments for adenosine-mediated bronchoconstriction, is that administration is direct to the lungs, or in situ to other tissues, organs or systems of the body. Additionally, a receptor protein itself is reduced in amount, rather than merely interacting with a drug, and toxicity is reduced. Other proteins that may be targeted with antisense agents for the treatment of lung conditions include, but are not limited to: CCR3 (chemokine) receptors, human  $A_2$ , adenosine receptor, human  $A_{2b}$  adenosine receptor, human IgE receptor  $\beta$ , human Fcepsilon receptor CD23 antigen, human histidine decarboxylase, human beta tryptase, human tryptase-I, human prostaglandi 1 D synthase, human cyclooxigenase-2, human eosinophil cationic protein, human eosinophil derived neurotoxin, human eosinophil peroxidase, human intercellular adhesion molecule-1 (ICAM-1), human vascular cell adhesion molecule-1 (VCAM-1), human endothelial leukocyte adhesion molecule-1 (ELAM 1), human P selectin, human endothelial monocyte activating factor, human IL-3, human IL-4, humar IL-5, human IL-6, human IL-8, human monocyte-derived neutrophil chemotactic factor, human neutrophil elastase, human neutrophil oxidase factor, human cathepsin G, human defensin 1, human defensin 3, human macrophage inflammatory protein-1-alpha, human muscarinic acetylcholine receptor HM3, human fibronectin, human GM-CSF, human tumor necrosis factor α, human leukotriene C4 synthase, human major basic protein, and human endothelin 1. Although not intended to be exclusive, a more extensive list of genes is provided below. Some of these act to alleviate the symptoms or reduce respiratory ailments and/or inflammation, for example, by "down regulation" of the adenosine A<sub>1</sub>, A<sub>2a</sub>, A<sub>2b</sub>, and/or A<sub>3</sub> receptors and CCR3, bradykinin 2B, VCAM (vascular cell adhesion molecule) and eosinophil receptors. These agents are preferably administered directly into the respiratory system, e.g., by inhalation or other means, so that they may reach the lungs without widespread systemic dissemination. This permits the use of substantially lower doses of the agent of the invention as compared with those administered by the prior art, systemically or by other generalized routes and, consequently, reduce undesirable side effects resulting from the agent=s widespread distribution in the body. The agent(s) of this invention has (have) been shown to reduce the amount of receptor protein expressed by the tissue. These agents, thus, rather than merely interacting with their targets, e.g. a receptor, lower the number of target proteins that other drugs may interact with. In this manner, the present agent(s) afford(s) extremely high efficacy with low toxicity. In these later targets, and in target genes in general, it is particularly imperative to eliminate or reduce the adenosine content of the corresponding anti-sense oligonucleotide to prevent their breakdown products from libera ing adenosine.

As used herein, the term "treat" or "treating" asthma refers to a treatment which decreases the likelihood that the subject administered such treatment will manifest symptoms of the lung disease. The term "downregulate' refers to inducing a decrease in production, secretion or availability (and thus a

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decrease in concentration) of the targeted intracellular protein. The present invention is concerned primarily with the treatment of human subjects. However, the agents and methods disclosed here may also be employed for veterinary purposes, such as is the case in the treatment of other mammals, such as cattle, horses, wild animals, zoo animals, and domestic animals, e. g. dogs and cats. Targeted proteins are preferably mammalian and more preferably of the same species as the subject being treated. In general, "anti-sense" refers to the use of small, synthetic oligonucleotides, resembling single-stranded DNA, to inhibit gene expression by inhibiting the function of the target messenger RNA (mRNA). Milligan, J. F. et al., J. Med. Chem. 35(14), 1923-1937 (1993). In the present invention, inhibition of gene expression of the A<sub>1</sub> or A<sub>3</sub> adenosine receptor is desired. Gene expression is inhibited through hybridization to coding (sense) sequences in a specific messenger RNA (mRNA) target by hydrogen bonding according to Watson-Crick base pairing rules. The mechanism of anti-sense inhibition is that the exogenously applied oligonucleotides decrease the mRNA and protein levels of the target gene or cause changes in the growth characteristics or shapes of the cells. Id. See, also Helene, C. and Toulme, J., Biochim. Biophys. Acta 1049, 99-125 (1990); Cohen, J. S. D., Ed., Oligodeoxynucleotides as Anti-sense Inhibitors of Gene Expression; CRC Press: Boca Raton, FL (1987). As used herein, "anti-sense oligonucleotide" is defined as a short sequence of synthetic nucleotide that (1) hybridizes to any coding sequence in an mRNA which codes for the targeted protein, according to hybridization conditions described below, and (2) upon hybridization causes a decrease in gene expression of the A<sub>1</sub> or A<sub>3</sub> adenosine receptor. The receptors discussed above are mere examples of the high power of the present technology. In fact, a large number of genes may be targeted in a similar manner by practicing the present methods, to significantly down-regulate or obliterate protein expression and observe any changes wrought to one or more functions within a system, e.g. the respiratory system and other lung disease associated targets. By means of example, in the respiratory system, the targets may be associated with difficulties of breathing, bronchoconstriction, inflammation, allergic rhynitis, chronic bronchitis, surfactant depletion, and others associated with diseases and conditions such as chronic obstructive pulmonary disease (COPD), pulmonary transplantation rejection, pulmonary infections, inhalation burns, Acute Respiratory Distress Syndrome (ARDS), cystic fibrosis, pulmonary fibrosis, adiation pulmonitis, tonsilitis, emphysema, dental pain, oral inflammation, joint pain, esophagitis, cancers afflicting the respiratory system either directly such as lung cancer, esophageal cancer, and the like, or ind rectly by means of metastases, among others. These functions are of great interest because of their association with respiratory dysfunction, as is the case in asthma, allergies, allergic rhinitis, pulmonary bronchoconstriction and hypertension, chronic obstructive pulmonary disease (COPD), pulmonary transplar tation rejection, pulmonary infections, allergy, asthma, cystic fibrosis (CF), Acute Respiratory Distress Syndrome (ARDS) as well as infantile and pregnancy-related RDS, cancer, etc., which either directly or by netastasis afflict the lung, the present anti-sense oligonucleotides may be directed to a list of target mRNAs, which includes the targets listed in Table 1 above, among others.

The oligos of this invention may be obtained by first selecting fragments of a target nucleic acid having at least 4 contiguous nucleic acids selected from the group consisting of G and C and/or having a specific type and/or extent of activity, and then obtaining a first oligonucleotide 4 to 60 nucleotides long which comprises the selected fragment and has a thymidine (T) nucleic acid content of up to and including about 15%, preferably, about 12%, about 10%, about 7%, about 5%, about 3%, about 1%, and more preferably no thymidine. The latter step may be conducted by obtaining a second oligonucleotide 4 to 60 nucleotides long comprising a sequence which is anti-sense to the selected fragment, the second oligonucleotide having an adenosine base content of up to and including about 15%, preferably about 12%, about 10%, about 7%, about 5%, about 3%, about 1%, and more preferably no adenosine. When the selected fragment comprises at least one thymidine base, an adenosine base may be substituted in the corresponding anti-sense nucleotide fragment with a universal base selected from the group consisting of heteroaromatic bases which bind to a thymidine base but have less than about bout 10%, preferably less than about 1%, and more preferably less than about 0.3% of the adenosine base agonist activity at the adenosine A<sub>1</sub>, A<sub>2a</sub>, A<sub>2b</sub> and A<sub>3</sub> receptors, and heteroaromatic bases which have no activity at the adenosine

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A<sub>2a</sub> receptor, when validating in the respiratory system. Other adenosine activities in other systems may be determined in other systems, as appropriate. The analogue heteroaromatic bases may be selected from all pyrimidines and purines, which may be substituted by O, halo, NH<sub>2</sub>, SH, SO, SO<sub>2</sub>, SO<sub>3</sub>, COOH and branched and fused primary and secondary amino, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alk oxy, alkenoxy, acyl, cycloacyl, arylacyl, alkynoxy, cycloalkoxy, aroyl, arylthio, arylsulfoxyl, halocycloalkyl, alkylcycloalkyl, alkenylcycloalkyl, alkynylcycloalkyl, haloaryl, alkylaryl, alkenylaryl, arylalkyn, arylalkynyl, arylcycloalkyl, which may be further substituted by O, halo, NH<sub>2</sub>, primary, secondary and tertiary amine, SH, SO, SO<sub>2</sub>, SO<sub>3</sub>, cycloalkyl, heterocycloalkyl and heteroaryl. The pyrimidines and purines may be substituted at all positions as is known in the art, but preferred are those which are substituted at positions 1, 2, 3, 4, 7 and/or 8. More preferred are pyrimi lines and purines such as theophylline, caffeine, dyphylline, etophylline, acephylline piperazine, bamifylline, enprofylline and xantine having the chemical formula

wherein R1 and R2 are independently H, alkyl, alkenyl or alkynyl and R3 is H, aryl, dicycloalkyl, dicycloalkenyl, dicycloalkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, O-cycloalkyl, O-cycloalkenyl, Ocycloalkynyl, NH<sub>2</sub>-alkylamino-ketoxyalkyloxy-aryl, mono and dialkylaminoalkyl-N-alkylamino-SO, aryl, among others. Similar modifications in the sugar are also embodiments of this invention. Reduced adenosine content of the anti-sense oligos corresponding to the thymidines (T) present in the target RNA serves to prevent the breakdown of the oligos into products that free adenosine into the system, e.g. the lung, brain, heart, kidney, etc., tissue environment and, thereby, to prevent any unwanted effects due to it. By means of examp e, the Nf6B transcription factor may be selected as a target, and its mRNA or DNA searched for low thymidine (T) or desthymidine (desT) fragments. Only desT segments of the mRNA or DNA are selected which, in turn, will produce desA anti-sense as their complementary strand. When a number of RNA de:T segments are found, the sequence of the anti-sense segments may be deduced. Typically, about 10 .o 30 and even larger numbers of desA anti-sense sequences may be obtained. These anti-sense sequences may include some or all desA anti-sense oligonucleotide sequences corresponding to desT segments of the mRNA of the target, such as anyone of those shown in Table 1 above, in Table 2 below, and others associated with functions of the brain, cardiovascular and renal systems, and many others. When this occurs, the anti-sense oligonucleotides found are said to be 100% A-free. For each of the original desA anti-sense oligonucleotide sequences corresponding to the target gene, e.g. the NF6B transcription factor, typically about 10 to 30 sequences may be found within the target gene or RNA which have a low content of thymidine (RNA). In accordance with this invention, the selected fragment sequences may also contain a small number of thymidine (RNA) nucleotides within the secondary or tertiary or quaternary sequences. In some cases, a large adenosine content may suffice to render the antisense oligonucleotide less active or even inactive against the target. In accordance with this invention, these so called "non-fully desA" sequences may preferably have a content of adenosine of less than about 15%, about 12%, about 10%, about 7%, about 5%, and about 2% adenosine. Most preferred is no adenosine content (0%). In some instances, however, a higher content of adenosine is acceptable and the oligonucleotides still fail to show detrimental "adenosine activity". A particular important embodiment is that where the adenosine nucleotide is "fixed" or replaced by a "Universal or alternative" base that may base-pair with similar or equal affinity to two or more of the four nucleotide present in natural DNA: A, G, C, and T.

A universal or alternative base is defined in this patent as any compound, more commonly an

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adenosine analogue. which has substantial capacity to hybridize to thymidine, while at the same time having reduced, or substantially lacking, ability to bind adenosine receptors or other molecules through which adenosine may exert an undesirable side effect in the experimental animal or in a cell system. Alternatively, adenosine analogs which completely fail to activate, or have significantly reduce ability for activating, adenosine receptors, such as the adenosine A1, A2b and/or A3 receptors, most preferably A1 receptors, and those that may even act as agonists of the adenosine A2a, receptor, may be used. One example of a universal base is α-deoxyribofuranosol-(5-nitroindole), and an artisan will know how to select others. This "fixing" step generates further novel sequences, different from those anti-sense to the ones found in nature, that permits the anti-sense oligonucleotide to bind, preferably equally well, with the target RNA. Other examples of universal or alternative bases are 2-deoxyribosyl-(5-nitroindole). Other examples of universal bases are 3 - nitropyrrole - 2' - deoxynucleoside, 5 - nitro-indole, 2 - deoxyribosyl -(5 - nitroindole), 2-deoxyribofuranosyl - (5-nitroindole), 2' - deoxyinosine, 2' -deoxynebularine, 6H, 8H-3,4-dihydropyrimidc [4, 5 - c] oxazine - 7 - one and 2 - amino - 6 -methoxy aminopurine. In addition to the above, Universal bases which may be substituted for any other base although with somewhat reduced hybridization potential, include 3 - nitropyrrole 2' - deoxynucleoside 2 - deoxyribofuranosyl - (5 nitroindole), 2' - de xyinosine and 2' - deoxynebularine (Glen Research, Sterling, VA). More specific mismatch repairs may be made using "P" nucleotide, 6H, 8H - 3, 4 - dihydropyrimido [4,5 - c] [1, 2] oxazin - 7 - one, which base pairs with either guanine (G) or adenine (A) and "K" nucleotide, 2 - amino - 6 - methoxyaminopuri 1e, which base pairs with either cytidine (C) or thymidine (T), among others. Others which are known in the art or will become available are also suitable. See, for example, Loakes, D. and Brown, D. M., Nucl. Acids Res. 22:4039-4043 (1994); Ohtsuka, E. et al., J. Biol. Chem.260(5):2605-2608 (1985); Lin, P.K.T. and Brown, D. M., Nucleic Acids Res. 20(19):5149-5152 (1992; Nichols, R. et al., Nature 369(6480): 492-493 (1994); Rahmon, M. S. and Humayun, N. Z., Mutation Research 377 (2): 263-8 (1997); Amosova, O., et al., Nucleic Acids Res. 25 (!0): 1930-1934 (1997); Loakes D. & Brown, D. M., Nucleic Acids Res. 22 (20): 4039-4043 (1994), the entire sections relating to universal bases and their preparation and use in nucleic acid binding being incorporated herein by reference. When non-fully desT sequences are found in the naturally occurring target, they typically are selected so that about 1 to 3 universal base subst tutions will suffice to obtain a 100% "desA" anti-sense oligonucleotide. Thus, the present method prov des either anti-sense oligonucleotides to different targets which are low in, or devoid of, A content, as well as anti-sense oligonucleotides where one or more adenosine nucleotides, e. g. about 1 to 3, or more, may be "fixed" by replacement with a "Universal" or "replacement" base. Universal bases are known in the art and need not be listed herein. An artisan will know which bases may act as universal bases, and replace them for A. Table 2 below provides a selected number of targets to which the agents of the invention are effectively applied. Others, however, may also be targeted.

35		Cancer Targets
	Transforming	Therapy
	Oncogenes	Targets
	ras	thymidylate synthetase
	src	thymidylate synthetase
40	my:	dihydrofolate reductase
	bel 2	thymidine kinase
		deoxycytidine kinase
		ribonucleotide reductase
	Angiogenesis factors	Adhesion Molecules
45	Oncogenes	Folate Pathway Enzymes
	DNA repair genes	(One Carbon Pool)
		Telomerase
		HMG CoA Reductase
		Farnesyl Transferase
50		Glucose-6-Phosphate Transferase

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A group of preferred targets for the treatment of cancer are genes associated with any of different types of cancers, or hose generally known to be associated with malignancies, whether they are regulatory or involved in the production of RNA and/or proteins. Examples are transforming oncogenes, including, but not limited to, ras, src, myc, and BCL-2, among others. Other targets are those to which present cancer chemotherapeutic agents are directed to, such as various enzymes, primarily, although not exclusively. thymidylate synthetise, dihydrofolate reductase, thymidine kinase, deoxycytidine kinase, ribonucleotide reductase, and the like. The present technology is particularly useful in the treatment of cancer ailments given that traditiona cancer therapies are fraught with the unresolved problem of selectively killing cancer cells while preserving normal living cells from the devastating effects of treatments such as chemotherapy, radiotherapy, and the like. The present technology provides the ability of selectively attenuating or enhancing a desirec pathway or target. This approach provides a significant advantage over standard treatments of cance because it permits the selection of a pathway, including primary, secondary and possibly tertiary targets, which are not generally expressed simultaneously in normal cells. Thus, the present agent may be administered to a subject to cause a selective increase in toxicity within tumor cells that, for instance, express all three targets while normal cells that may expresses only one or two of the targets will be significantly less affected or even spared. A group of preferred targets for the treatment of cancers are genes associated with different types of cancers, or those generally known to be associated with malignancies, whether they are regulatory or involved in the production of RNA and/or proteins. Examples are transforming oncogenes, including, but not limited to, ras, src, myc, and BCL-2, among others. Other targets are those to which present cancer chemotherapeutic agents are directed to, such as various enzymes, primarily, although not exclusively, thymidylate synthetase, dihydrofolate reductase, thymidine kinase, deoxycytidine kinase, ribonucleotide reductase, and the like.

In one embodiment, at least one of the mRNAs to which the oligo of the invention is targeted encodes a protein such as transcription factors, stimulating and activating factors, intracellular and extracellular receptors and peptide transmitters in general, interleukins, interleukin receptors, chemokines, chemokine receptors, endogenously produced specific and non-specific enzymes, immunoglobulins, antibody receptors, central nervous system (CNS) and peripheral nervous and non-nervous system receptors, CNS and peripheral nervous and non-nervous system peptide transmitters, adhesion molecules, defensines, growth factors, vasoactive peptides and receptors, and binding proteins, among others; or the mRNA is corresponding to an oncogene and other genes associated with various diseases or conditions. Examples of target proteins are eotaxin, major basic protein, preproendothelin, eosinophil cationic protein, P-selectin, STAT 4, MIP-1α, MCP-2, MCP-3, MCP-4, STAT 6, c-mas, NF-IL-6, cyclophillins, PDG2, cyclosporin A-binding protein, FK5-binding protein, fibronectin, LFA-1 (CD11a/CD18), PECAM-1, C3bi, PSGL-1,CD-34, substance P, p150,95, Mac-1 (CD11b/CD18), VLA-4, CD-18/CD11a, CD11b/CD18, C5a, CCR1, CCR2, CCR4, CCR5, and LTB-4, among others. Others are, however, suitable, as well. In another embodiment, at least one of the mRNAs to which the oligo is targeted encodes intracellular and extracellular receptors and peptide transmitters such as sympathomimetic receptors, parasympathetic receptors, GABA receptors, adenosine receptors, bradykinin receptors, insulin receptors, glucagon receptors, prostaglandin receptors, thyroid receptors, androgen receptors, anabolic receptors, estrogen receptors, progesterone receptors, receptors associated with the coagulation cascade, adenohypophyseal receptors, adenohypophyseal peptide transmitters, and histamine receptors (HisR), among others. However others are also contemplated. The encoded sympathomimetic receptors and parasympathomimetic receptors include acetylcholinesterase receptors (AcChaseR) acetylcholine receptors (AcChR), atropine receptors, muscarin c receptors, epinephrine receptors (EpiR), dopamine receptors (DOPAR), and norepinephrine receptors (NEpiR), among others. Further examples of encoded receptors are adenosine A receptor, adenosine A2B receptor, adenosine A3 receptor, endothelin receptor A, endothelin receptor B, IgE high affinity receptor, muscarinic acetylcholine receptors, substance P receptor, histamine receptor, CCR-1 CC chemokine receptor, CCR-2 CC chemokine receptor, CCR-3 CC chemokine receptor (Eotaxin Receptor), interleukin-1β receptor (IL-1βR), interleukin-1 receptor (IL-1R), interleukin-1β receptor (IL-

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1βR), interleukin-3 receptor (IL-3R), CCR-4 CC chemokine receptor, cysteinyl leukotriene receptors, prostanoid receptors, GATA-3 transcription factor receptor, interleukin-1 receptor (IL-1R), interleukin-4 receptor (IL-4R), interleukin-5 receptor (IL-5R), interleukin-8 receptor (IL-8R), interleukin-9 receptor (IL-9R), interleukin-11 receptor (IL-11R), bradykinin B2 receptor, sympathomimetic receptors, parasympathomimet c receptors, GABA receptors, adenosine receptors, bradykinin receptors, insulin receptors, glucagon receptors, prostaglandin receptors, thyroid receptors, androgen receptors, anabolic receptors, estrogen receptors, progesterone receptors, receptors associated with the coagulation cascade, adenohypophyseal receptors, and histamine receptors (HisR). Others are also contemplated even though not listed herein. The encoded enzymes for development of the oligos of the invention include synthetases, kinases, oxidases, phosphatases, reductases, polysaccharide, triglyceride, and protein hydrolases, esterases, elastases, and , polysaccharide, triglyceride, lipid, and protein synthases, among others. Examples of target enzymes are tryptase, inducible nitric oxide synthase, cyclooxygenase (Cox), MAP kinase, eosir ophil peroxidase, β2-adrenergic receptor kinase, leukotriene c-4 synthase, 5lipooxygenase, phosphodiesterase IV, metalloproteinase, tryptase, CSBP/p38 MAP kinase, neutrophil elastase, phospholipise A2, cyclooxygenase 2 (Cox-2), fucosyl transferase, chymase, protein kinase C, thymidylate synthetase, dihydrofolate reductase, thymidine kinase, deoxycytidine kinase, and ribonucleotide reductase, among others. Any enzyme associated with a disease or condition, however, is suitable as a target for this invention. Suitable encoded factors for application of this invention are, among others, Nf6B transc iption factor, granulocyte macrophage colony stimulating factor (GM-CSF), AP-1 transcription factor, GATA-3 transcription factor, monocyte activating factor, neutrophil chemotactic factor, granulocyte/macrophage colony-stimulating-factor (G-CSF), NFAT transcription factors, platelet activating factor, tumor necrosis factor  $\alpha$  (TNF  $\alpha$ ), and basic fibroblast growth factor (BFGF). Additional factors are also within the invention even though not specifically mentioned. Suitable adhesion molecules for use with this invention include intracellular adhesion molecules 1 (ICAM-1), 2 (ICAM-2) and 3 (ICAM-3), vascular cellular adhesion molecule (VCAM), endothelial leukocyte adhesion molecule-1 (ELAM-1), neutrophil adherence receptor, mad CAM-1, and the like. Other known and unknown factors (at this time) may also be targeted herein. Among the cytokines, lymphokines and chemokines preferred are interleukin-1 (II.-1), interleukin-1β (IL-1β), interleukin-3 (IL-3), interleukin-4 (IL-4), interleukin-5 (IL-5), interleukin-8 (IL-8), interleukin-9 (IL-9), interleukin-11 (IL-11), CCR-5 CC chemokine, and Rantes. Others, however, may also be targeted, as they are known to be involved in specific diseases or conditions to be treated, or for their generic activities, such as inflammation. Examples of defensins for the practice of this invention are de ensin 1, defensin 2, and defensin 3, and of selectins are  $\alpha 4\beta 1$  selectin,  $\alpha 4\beta 7$  selectin, LFA-1 selectin, E-se ectin, P-selectin, and L-selectin. Examples of oncogenes, although not an all inclusive list, are ras, src, myc, and bcBCL. Others, however, are also suitable for use with this invention.

The agents administered in accordance with this invention are preferably designed to be anti-sense to target genes and/or mRNAs related in origin to the species to which it is to be administered. When treating humans, the agents are preferably designed to be anti-sense to a human gene or RNA. The agents of the invention encompass oligonucleotides which are anti-sense to naturally occurring DNA and/or RNA sequences, fragments thereof of up to a length of one (1) base less than the targeted sequence, preferably at least about 7 nucleot des long, oligos having only over about 0.02%, more preferably over about 0.1%, still more preferably over about 1%, and even more preferably over about 4% adenosine nucleotides, and up to about 30%, more preferably up to about 15%, still more preferably up to about 10% and even more preferably up to about 5%, adenosine nucleotide, or lacking adenosine altogether, and oligos in which one or more of the adenosine nucleotides have been replaced with so-called universal bases, which may pair up with thymidine nucleotides but fail to substantially trigger adenosine receptor activity. Examples of human sequences and fragments, which are not limiting, of anti-sense oligonucleotide of the invention are the following fragments as well as shorter segments of the fragments and of the full gene or mRNA coding sequences, exons and intron-exon junctions encompassing preferably 7, 10, 15, 18 to 21, 24, 27, 30, n-1 nucleotides for each sequence, where n is the sequence=s total number of nucleotides. These fragments

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may be selected from any portion of the longer oligo, for example, from the middle, 5'- end, 3'- end or starting at any other site of the original sequence. Of particular importance are fragments of low adenosine nucleotide content, that is, those fragments containing less than or about 30%, preferably less than or about 15%, more preferably less than or about 10%, and even more preferably less than or about 5%, and most preferably those devoid of adenosine nucleotide, either by choice or by replacement with a universal base in accordance with this invention. The agent of the invention includes as a most preferred group sequences and their fragments where one or more adenosines present in the sequence have been replaced by a universal base (B), as exemplified here. Similarly, also encompassed are all shorter fragments of the B-containing fragments designed by substitution of B(s) for adenosine(s) (A(s)) contained in the sequences, fragments thereof o segments thereof, as described above. A limited list of sequences and fragments is provided below.

Some of the examples of anti-sense oligonucleotide sequence fragments target the initiation codon of the respective gene, and in some cases adenosine is substituted with a universal or alternative base adenosine analogue denoted as "B", which lacks ability to bind to the adenosine  $A_1$  and/or  $A_3$  receptors. In fact, such replacement nucleotide acts as a "spacer". Many of the examples shown below provide one such sequence and many fragments overlapping the initiation codon, preferably wherein the number of nucleotides n is about 7, about 10, about 12, about 15, about 18, about 21 and up to about 28, about 35, about 40, about 50, about 60.

#### Human Receptor-related Antisense Polynucleotide

5'-GGCGGCCTGG AAAGCTGAGA TGGAGGGCGG CATGGCGGGC ACAGGCTGGG C TGCTTTTCT TTTCTGGGCC TCTGTGGTCT GTT1TTTTCT GGCCCTGCTG GGGCGCTCTC CGCCGCCCGC CTGGCTCCCG GBGCCCBTGB TGGGCBTGCC GTCGTTCTTG CCCTCCTTTG GCTGCCGTGC CCGCTCCCCG GCCTCCTGGC GGGTGGCCGT TGGGCCCGTG TTCCCCTGGG GCCTGGGGCT CCCTTCTCTC GCCCTTCTTG CTGGGCCTCT GCTGCTGCTG GTGCTGTGGC CCCCGTACA CCGAGGAGCC CATGATGGGC ATGCCACAGA CGACAGGCGT BCBCCGBGGB CGC GCG GGG CCC CTC CGG TCC GTT CGC GCC CGC GCG GGG CCC CTC CGG TCC CGG GTC GGG GCC CCC CCC CGG GCG CCC CCT CCC CTC TTG CTC GGG TCC CCG TG ACA GCG CGT CCT GTG TCT CCA GCA GCA TGG CCG GGC CAG CTG GGC CCC BCB GCG CGT CCT GTG TCT CCB GCB GCB TGG CCG GGC CBG CTG GGC CCC ACA GAG CAG TGC TGT TGT TGG GCA TCT TGC CTT CCC AGG G BCB GBG CB TGC TGT TGT TGG GCB TCT TGC CTT TTC ATT AAC CGA GCT GT BTT TGC TCT CCT BTT BCT TTC TGT GTC CBT TTT TTC BTT BBC CGB GCT GT GCC TCT TGC TCT GGG CCT GGC TGT GGC CGT GGT TGG GGG TCT TC GCT GCC TCC GTT TGG GTG GC TCT CTG AAT ATT GAC CTT CCT CCA TGG CGG TCC TGC TTG GAT TCT CCC GA TCT CTG BBT BTT GBC CTT CCT CCB TGG CGG TCC TGC TTG GBT TCT CCC GB GCC TTT CCT GGT TCT CTT GTT GTT GTT TTT GGG GTT TGG CTT ACA GTA GAG TAG GGGI ATT CCA TGG CAG GAG CCA TCT TCT TCA TGG ACT CC TTC AAG GAG ACC TTA GGT TTC TGA GGG ACT GCT AAC ACG CCA TCT GGA GC BCB GTB GBG TBG GGG BTT CCB TGG CBG GBG CCB TCT TCT TCB TGG BCT CC TTC BBG GBG BCC TTB GGT TTC TGB GGG BCT GCT BBC BCG CCB TCT GGB GC GTT GTT TTT GGG GTT TGG CTT GCC TTT CCT GGT TCT CTT BCB GTB GBG TBG GGG BTT CCB TGG CBG GBG CCB TCT TCT TCB TGG BCT CC TTC BBG GBG BCC TTB GGT TTC TGB GGG BCT GCT BBC BCG CCB TCT GGB GC GCC TGT GTC TGT CCT CCT GCT TCG TTC CTC TCG TTC CTG CTT GGT GCC CTT GCC G GTC CTG CTC CGG GCT GTG BGB CCC GGB CC() BCB GGC CGT GGT TGG GGG TCT TC GCT GCC TCC GTT TGG GTG GC GAT CTC TGA ATA TTGA CCT TCC A'G GCG GTC CTG CTT GGA GBT CTC TGB BTB TTGB CCT TCC BTG GCG GTC CTG CTT GGB TCT GGG GTG TCC TGG CCT TCG TGG TTC CTC TTC CTT CGT TTG CCG TCC GCG GGG GCC CCC GGG CCT GGC 

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CTC CTG GTC GCG (TT GTC GTT TTG GGG CCG GCT TTG CCC GCC TCC CGG CGC CTG GCC CGG CC TTC CTG GGC TGC GTG CGC (ITT CTG TTC TTC CTG GCT CTG GGG TGT CCT GGC CTT CGT GGT TCC TCT TCC TTC GTT TGC CGT CCG CGG GGG CCC CCG GGC CT GGC TGC GCT CCT GCC CCG CCT CTT TCC CGG GCT CTT GCG GAC AGG GCA GGG CGA TCA GGA GCA GCG TGA GCC AAA GGA GGA CCA TCG GGA ACG CAG CTC CGG AAC GCA GGA CAG AGG TGC C GC BGG BGB CBG GGC BGG GCG BTC BGG BGC BGC GTG BGC CBB BGG BGC BCC BTC GGG BBC GCB GCT CCG GBB CGC BGG BCB GBG GTG CC TCT GCC CTG TCC GCC GGC TCT TCG GTG GCT CGG CCC CGC TCC TIG TCT TGC CGC GGG TTG GTT CCT GGG CCT GGT TCT TGC GGG CGT TTC GGT CTG GCT GGT CTG GGC CCG CGG TGC GGC GGG TGG CTT GCT GTT CTG CCT GGG CTC TCC CCT CTC CTT TTC CGG GCG CTC GTG CCT GGT CCG CTC CCT GGG GGT GCT CCT TCC CTT TCC CCG CTC GTG GGG TTT GCG TCC CTG TGC CCC T°T CCT CTG CTG GGT CCC CCT CCC GTT CCA AGC TGC ACC GCA CAG ACC GGC GCT ACA GGA CAG AGC CAG GCA AGC ACC CAT GGG GAT CCA GGC CCA GCT GTT CCB BGC TGC BCC GCB CBG BCC GGC GCT BCB GGB CBG BGC CBG GCB BGC BCC CBT GGG GBT CCB GGC CCB GCT G CTCAGTGGCC CCCAAAAGGA TGAGTAATAC ATGCGCCACG ATGATCATAT CCTTTTTACT ATGAGGCCGT GTCTGTCGTG GTGTGTCTTT GCTGTGCCCT GCCTCTCTGC GGGGGTGGCT TCCTGCCGCG TCTCTGGGCC GTCCCGTCCC GCGCCGGGGC CTGTCCGCCT CTGCGGGCGC TGTCTCCTGG CTTGTCTTCC GGCTCTTCTG CTGGGGTGGG GGGGGTTTCT GGCCGTGGGG GTCTTGCCTG GCCTCCGGGC TCCTGCTTGT CTTGCCTTCC TTCTCTGGTC GGTTGTGGCT CGGGGCTCCG TGGGTCCCTG GCGCCCGTTT GTGTTTTGTC TTTTCCCCTG GCGTCCCTGT GCCCCTCTCC TCTCCTTCCT CTGCTTCTCG CTCTCCTTTG TGGGGCCCTC CCTGCTGCTC TTGGTTTTGG GCTTTTTTC TCTTCCTCT TTTTCGTGCG TGGGCCTCC GCACGCCTCT TGCCACCTCC TGCGCAGGGC AGCGCCTTGG GGCCAGCGC GCTCCCGGCG CGGCCAGCAG GGCAGCCAGC AGCGCGCAGC CGACGGCCAG CATGCTTCCT CCTCGGCTAC CACTCCATGG TCCCGCAGAG GCGGACAGGC GCBCGCCTC TTGCCBCCTC CTGCGCBGGG CBGCGCCTTG GGGCCBGCGC CGCTCCCGGC GCGGCCBGCB GGGCBGCCBG CBGCGCGCBG CCGBCGCCB GCBTGCTTCC TCCTCGGCTB CCBCTCCBTG GTCCCGCBGB GGCGGBCBGG C GGGGTGTGCG CTTCIGCGCTC CCGTGCTCGG TTCTCTGTCT CCCGGTCCCC CTTGCCTGGC GTCTCGGGCC TTCGTCCTCT TCCTCTTCTT CCTTCCGCTC CGTGGGGGCT GCTTGGTGGG GGCCTGTGCCT CGGGGTCCCG GGGCTTCTGG CCCTTGCCGT TCATGGTGGC TAGGTGGGGC GTTCBTGGTG GCTBGGTGGG GC GGG GTG GGT BGG CCG TGT CTG G3GGTT GGC CBT GTT GGT TGC CTCT TGG TGC TGC GCC GGG CGCG TCT TGG CTT TCT TGGCG CTG GCG GGG GGG CCT CCTGCT CTG TGG CTG GGC GTT CCT TGG TGT TCT GGG TGGTGG CGG GCG TGG TGG CCT CTG TCGGGGG CCC GCG GCT GCB GGG GTTG CCT GTC TGC TTC GTCCTT TGC GCT CCC GGG CCG CCGGG GTG GGT AGG CCG TGT CTG GGGGTT GGC CAT GTT GGT TGC CGGG CCC GCG GCT GCA GGG G ACAGGGGCTG TAATCTTCATC TGCAGGTGGC ATGCCAGTGA AATTTAGATC ATCAAAATCC CACATCTGTG GATCTGTAAT ATTTGACATG TCCTCTTCAG TTTCAGCAAT GGTTTGATCT AACTGAAGCA CCGGCCAGGB CBGGGGCTGT BBTCTTCBTC TGCBGGTGGC BTGCCBGTGB BBTTTBGBTC BTCBBBBTCC CBCBTCTGTG GBTCTGTBBT BTTTGBCBTG TCCTCTTCBG TTTCBGCBB TGGTTTGBTC TBBCTGBBGC BCCGGCCBGG TGGCTCGGTG CTTCTGCCCC TGTTGTTGCG GCGCTCGGTT GGTGTGGCCC CTGTGGTGCT TCGTTTCCCC CTCTTTCTCT TTGTTCGGGG GTTCTTGTGG CGGGCTGCTT GTCTCGTTCC GCCCTGTCGG GCGGGAAGCC TCTCTCCTCT CCCCAGATC CGCGACAGGC CGCAGGCAAG AACCAGCGCA ACCAGGGCGC GTCCGCACAG ACTTGGAGGC GGCTGCATGC TGCTACCTGC TCCAGAAGCG TCCGGTGGCC GCCGCGCC CTGTCGGGCG GGBBGCCTCT CTCCICTCCC CBGBTCCGCG BCBGGCCGCB GGCBBGBBCC BGCGCBBCCB GGGCGCGTCC GCBCBGBCTT GGBGGCGGCT GCBTGCTGCT BCCTGCTCGGGCG GGBBGCCTCCG GTGGCCGCCG CGCGTCCGGT GGCCGCCGCG CCTCTCTCCT CTCCCCGTGG CCCTGTCGGG CGGGTCCTGC CGTCCTGTCT CCTTTTCTTT TGCTGTCTTG TCTTCCCGTC TCTGCTTT GTCTGTCCTC CCCGTCTCCT CCCACTGCTT CTCCCGGGGG





	CGTGGGTGCC	CTGGTCATCC	CCCTCGCCAT	CCTCATCAAC	ATTGGGCCAC	AGACCTACTT	CCACACCTGC
	CTCATGGTTG	CCTGTCCGGT	CCTCATCCTC	ACCCAGAGCT	CCATCCTGGC	CCTGCTGGCA	ATTGCTGTGG
	ACCGCTACCT	CCGGGTCAAG	ATCCCTCTCC	GGTACAAGAT	GGTGGTGACC	CCCCGGAGGG	CGGCGGTGGC
	CATAGCCGGC	TGCTGGATCC	TCTCCTTCGT	GGTGGGACTG	ACCCCTATGT	TTGGCTGGAA	CAATCTGAGT
	${\tt GCGGTGGAGC}$	GGGCCTGGGC	AGCCAACGGC	AGCATGGGGG	AGCCCGTGAT	${\tt CAAGTGCGAG}$	TTCGAGAAGG
	TCATCAGCAT	GGAG'TACATG	GTCTACTTCA	ACTTCTTTGT	GTGGGTGCTG	CCCCCGCTTC	TCCTCATGGT
	CCTCATCTAC	CTGGA GGTCT	TCTACCTAAT	CCGCAAGCAG	CTCAACAAGA	AGGTGTCGGC	CTCCTCCGGC
	GACCCGCAGA	AGTACTATGG	GAAGGAGCTG	AAGATCGCCA	AGTCGCTGGC	CCTCATCCTC	TTCCTCTTTG
	CCCTCAGCTG	GCTGCCTTTG	CACATCCTCA	ACTGCATCAC	CCTCTTCTGC	CCGTCCTGCC	ACAAGCCCAG
)	CATCCTTACC	TACATTGCCA	TCTTCCTCAC	GCACGGCAAC	TCGGCCATGA	ACCCCATTGT	CTATGCCTTC
	CGCATCCAGA	AGTTCCGCGT	CACCTTCCTT	AAGATTTGGA	ATGACCATTT	CCGCTGCCAG	CCTGCACCTC
	CCATTGACGA	GGATCTCCCA	GAAGAGAGC	CTGATGACTA	GACCCCGCCT	TCCGCTCCCA	CCAGCCCACA
	TCCAGTGGGG	TCTC# GTCCA	GTCCTCACAT	GCCCGCTGTC	CCAGGGGTCT	CCCTGAGCCT	GCCCCAGCTG
	GGCTGTTGGC	TGGGC GCATG	GGGGAGGCTC	TGAAGAGATA	CCCACAGAGT	GTGGTCCCTC	CACTAGGAGT
	TAACTACCCT	ACACCTCTGG	GCCCTGCAGG	AGGCCTGGGA	GGGCAAGGGT	CCTACGGAGG	GACCAGGTGT
	CTAGAGGCAA	CAGTGTTCTG	AGCCCCCACC	TGCCTGACCA	TCCCATGAGC	AGTCCAGCGC	TTCAGGGCTG
	GGCAGGTCCT	GGGGA GGCTG	AGACTGCAGA	GGAGCCACCT	GGGCTGGGAG	AAGGTGCTTG	GGCTTCTGCG
	GTGAGGCAGG	GGAGTCTGCT	TGTCTTAGAT	GTTGGTGGTG	CAGCCCCAGG	ACCAAGCTTA	AGGAGAGGAG
					ATGCACTGGC		
i	GCCAGAGGCA	GCTA# GGGGC	AGGAATCAAG	GAGCCTCCGT	TCCCACCTCT	GAGGACTCTG	GACCCCAGGC
	CATACCAGGT	GCTAGGGTGC	CTGCTCTCCT	TGCCCTGGGC	CAGCCCAGGA	TTGTACGTGG	GAGAGGCAGA
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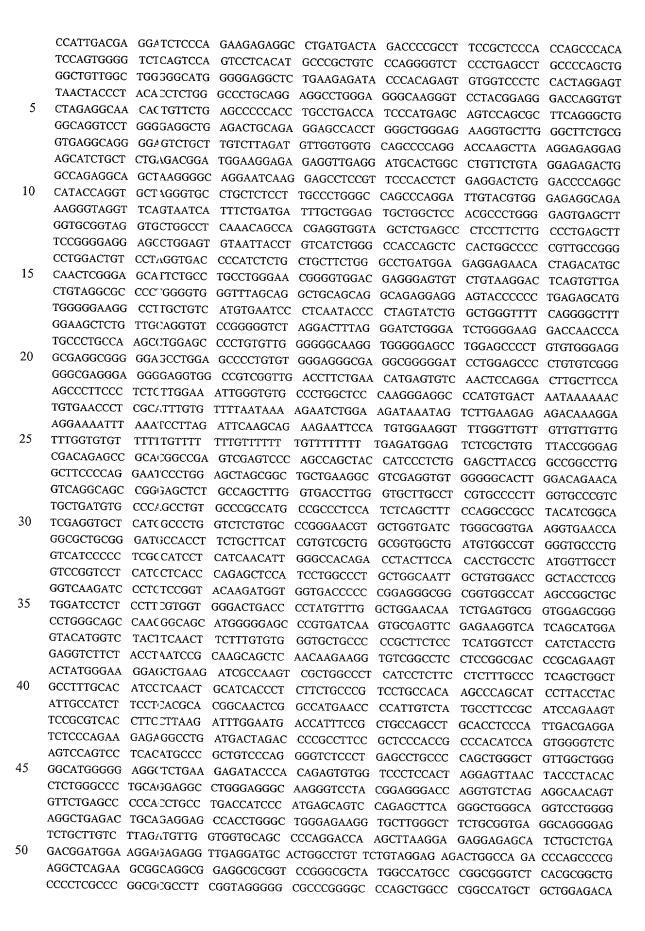


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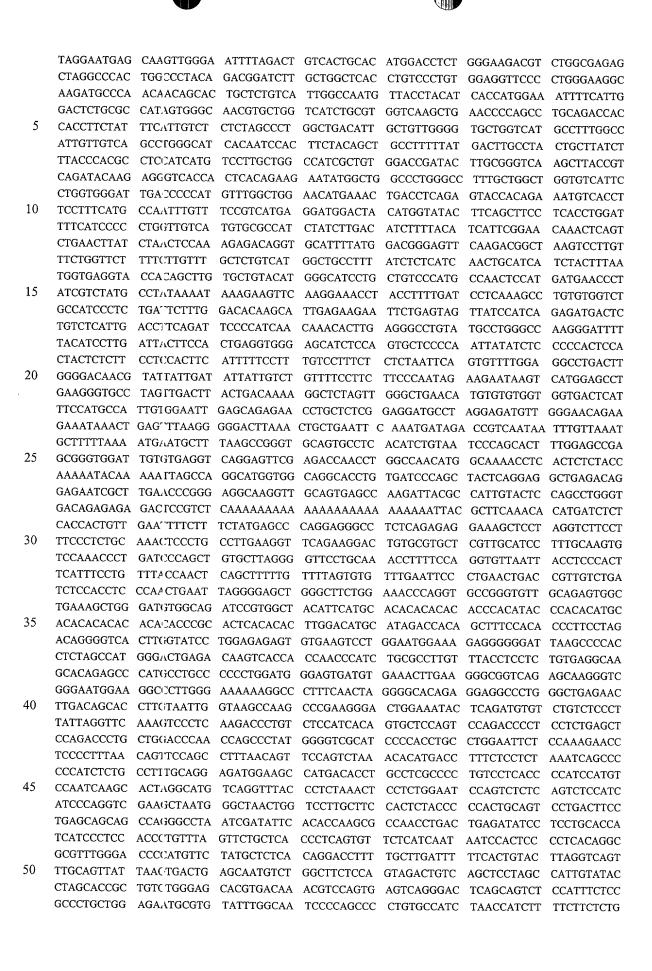


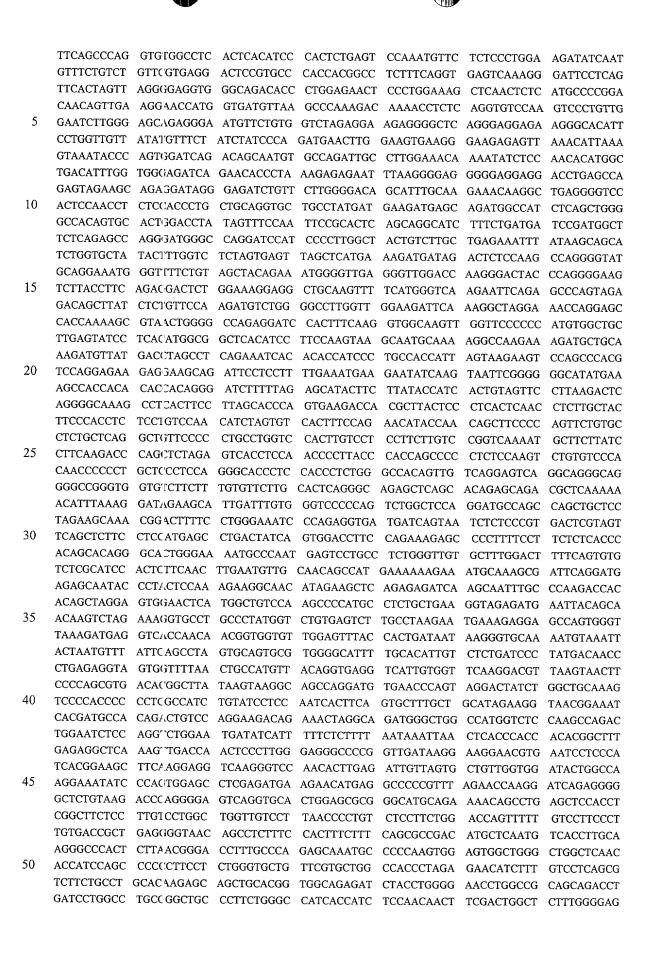


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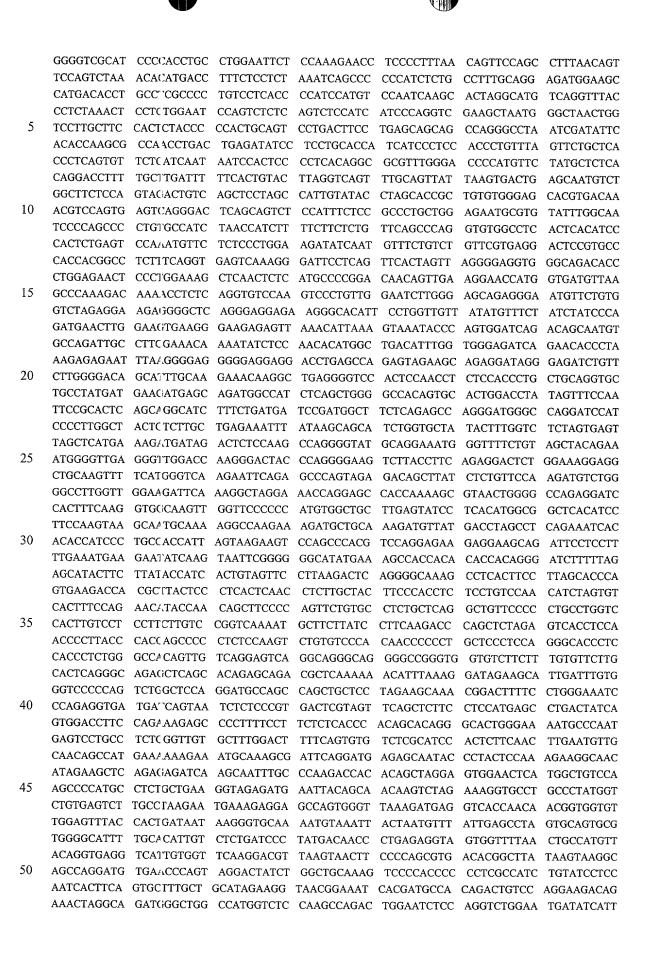


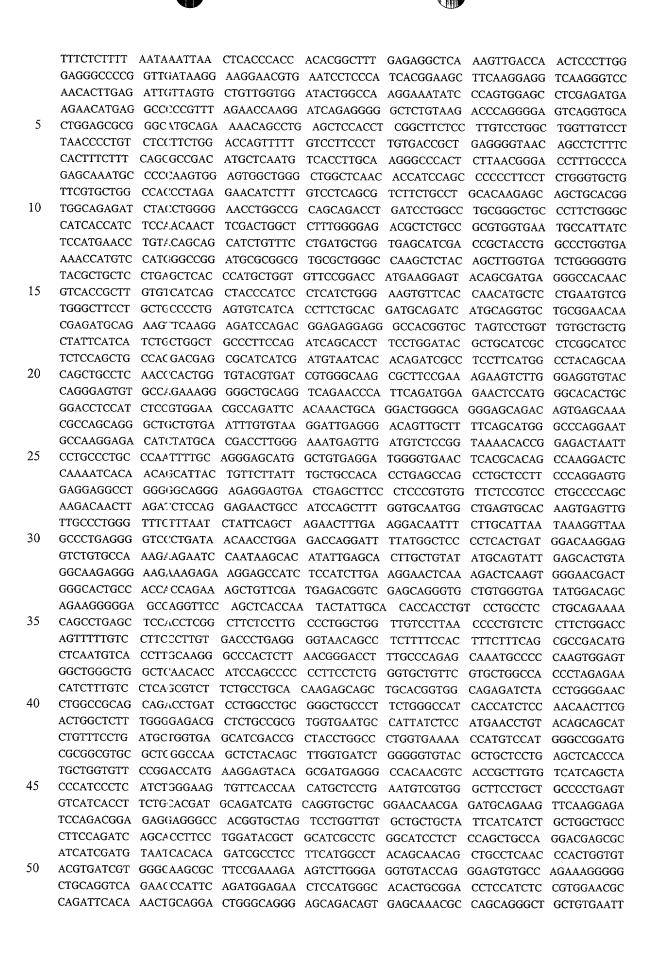




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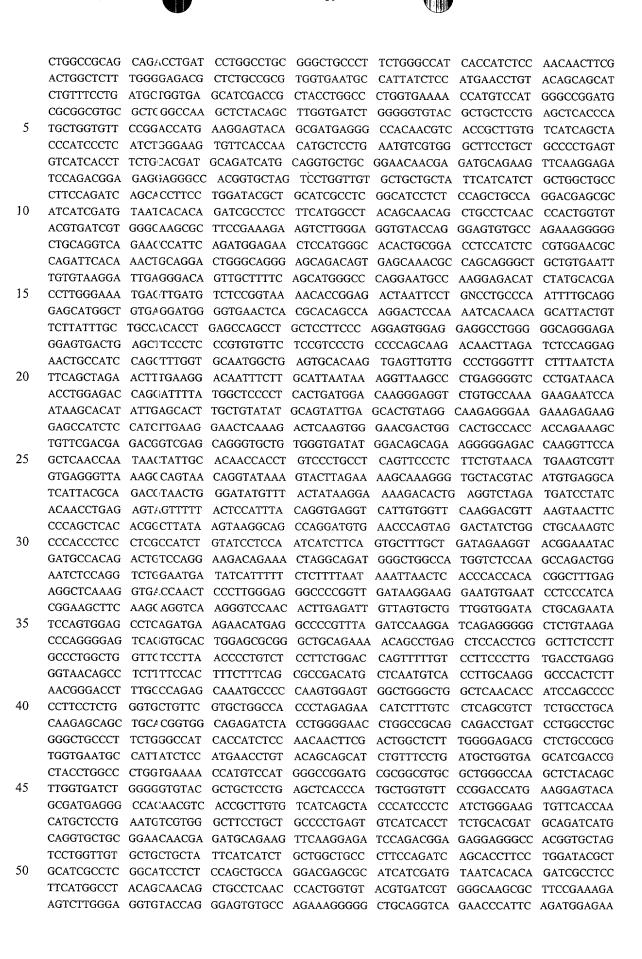
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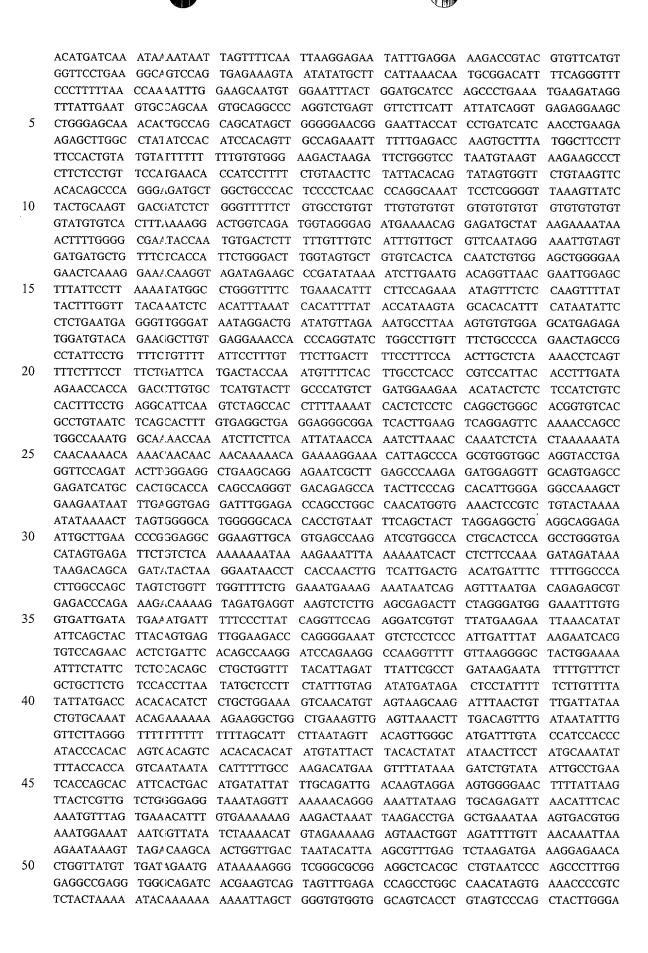


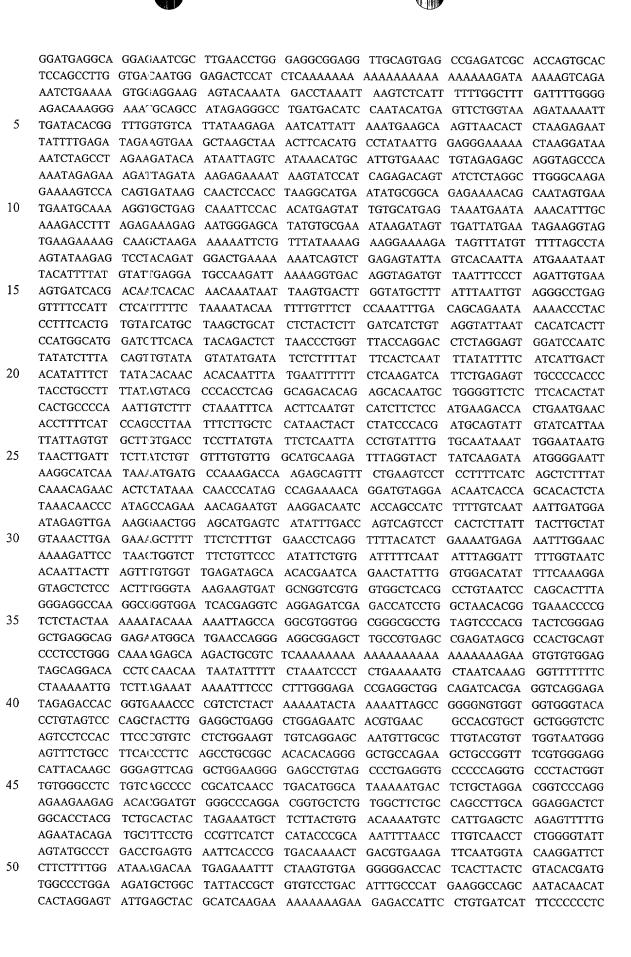
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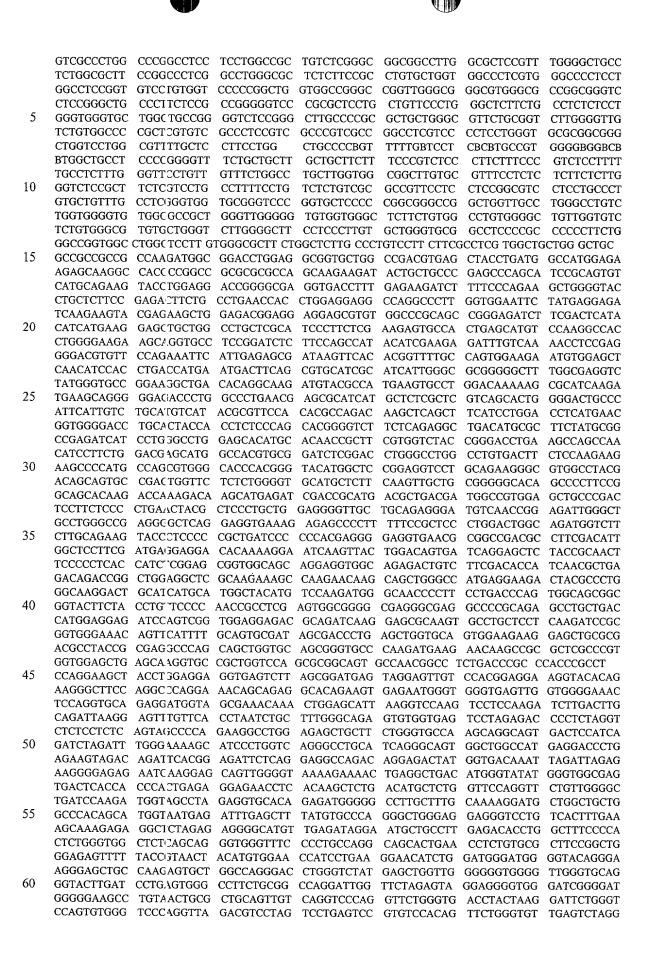


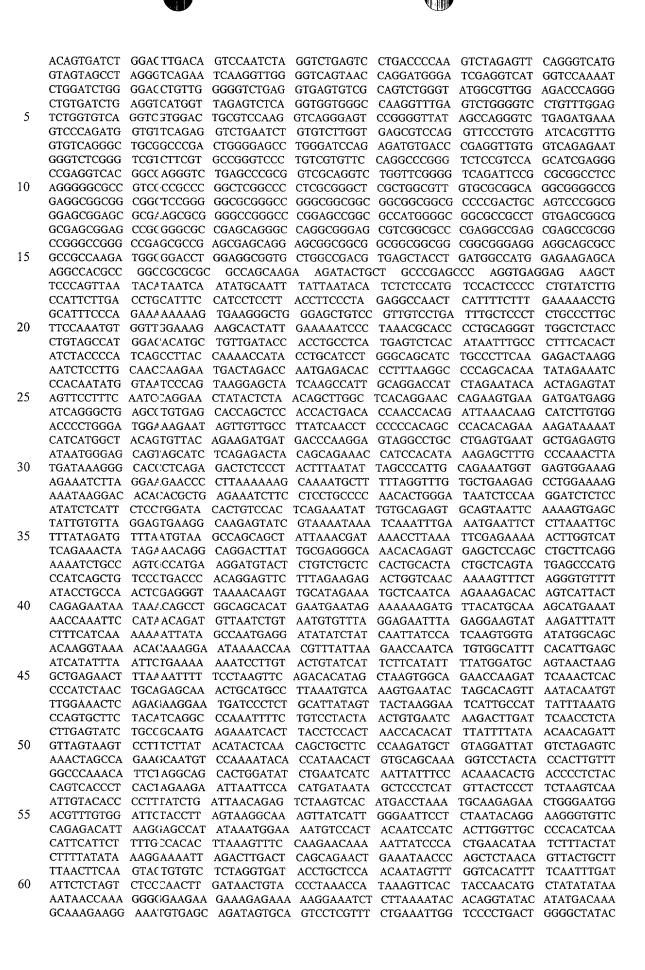
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## 0 Human Enzyme-related Antisense Polynucleotide



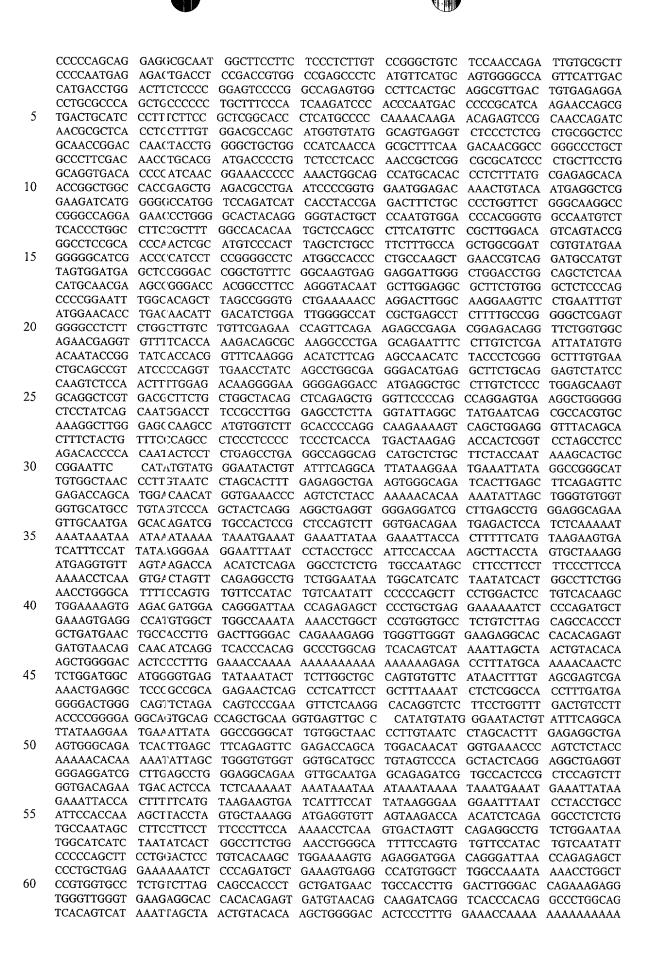






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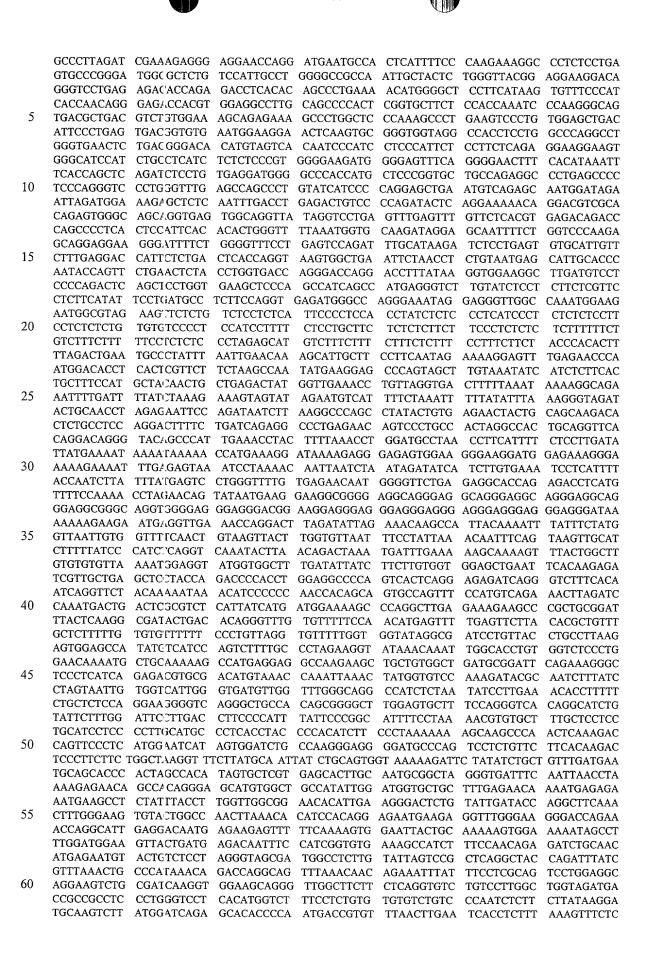


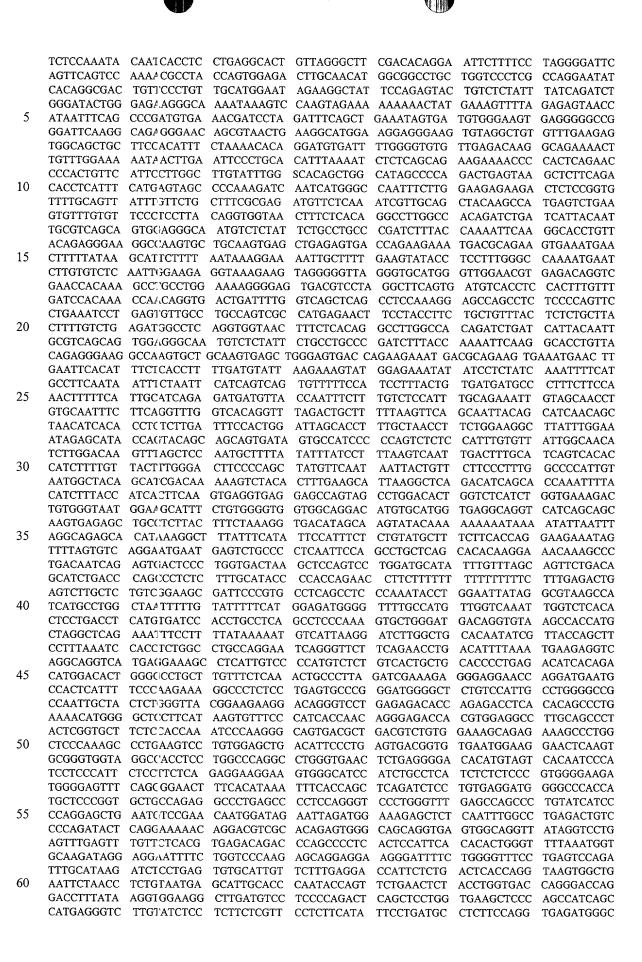
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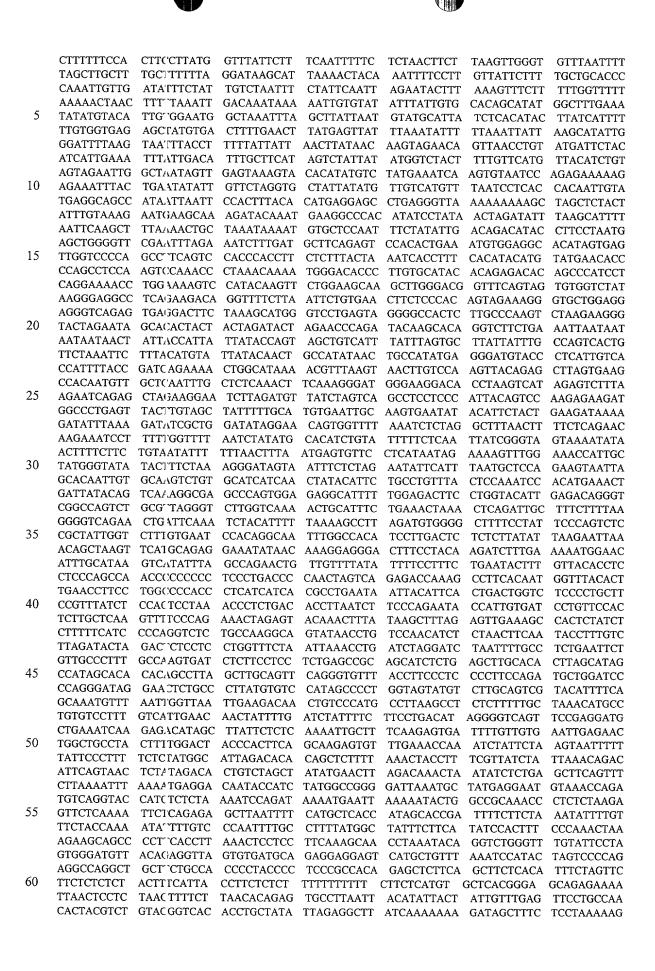
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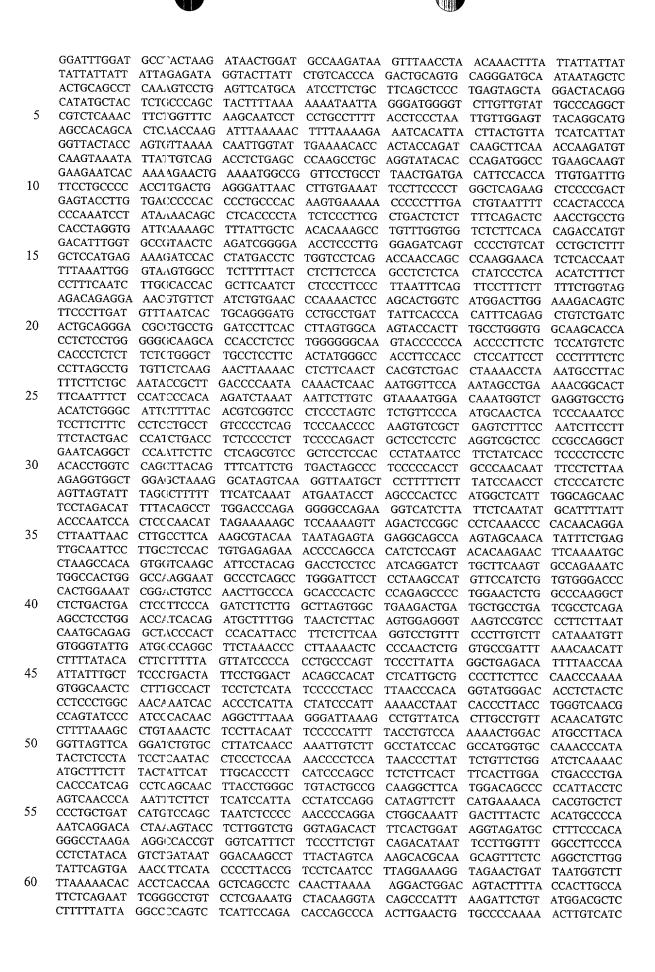


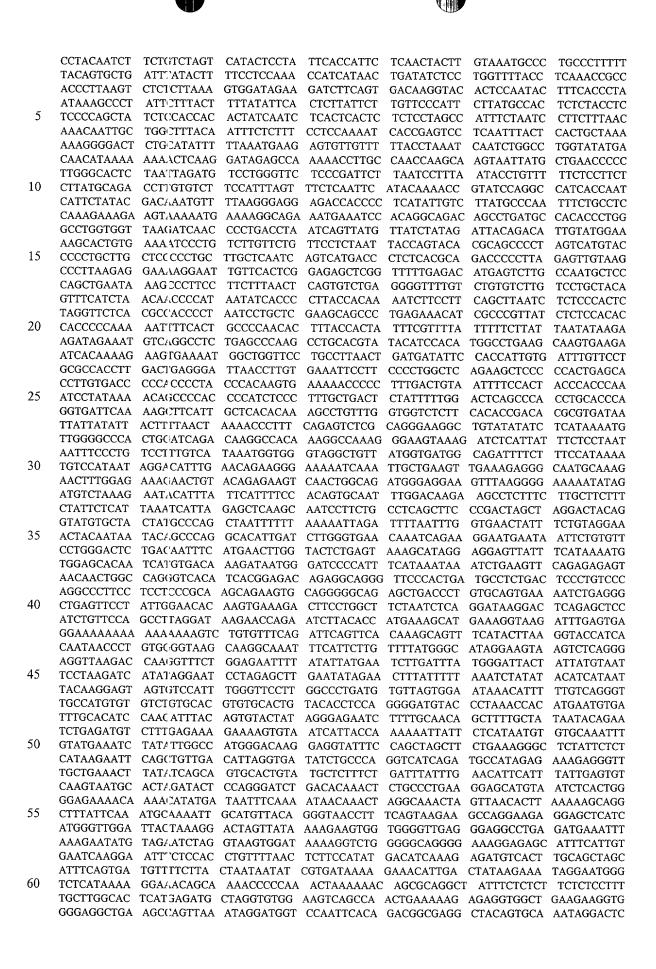
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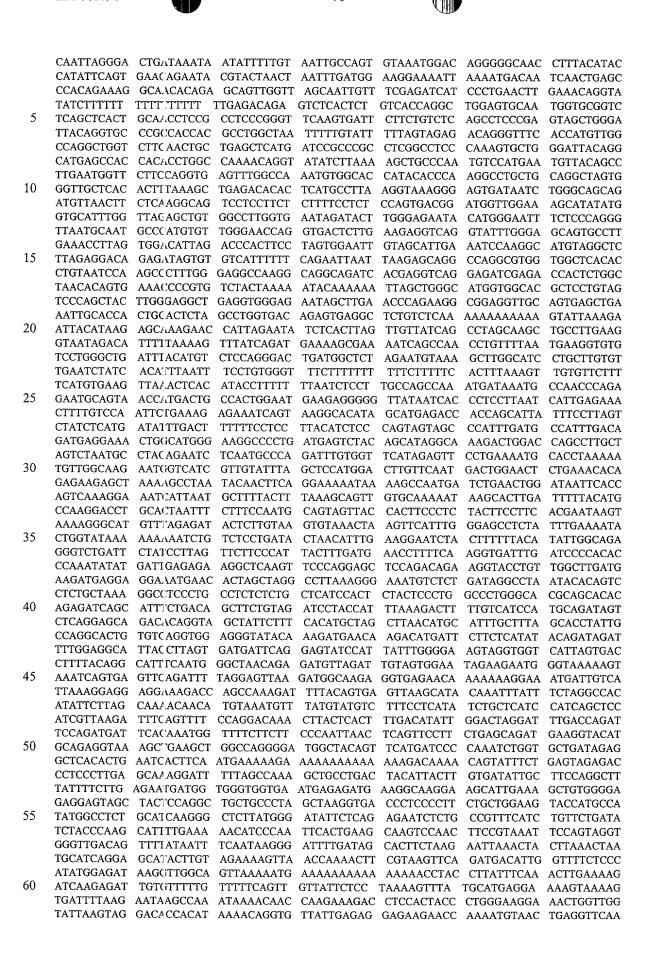




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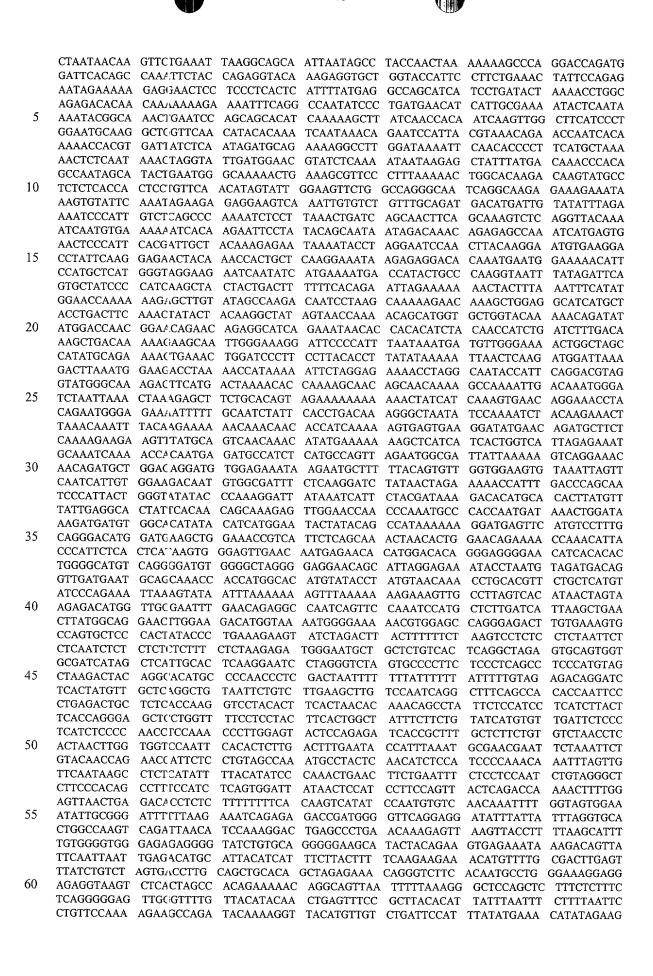




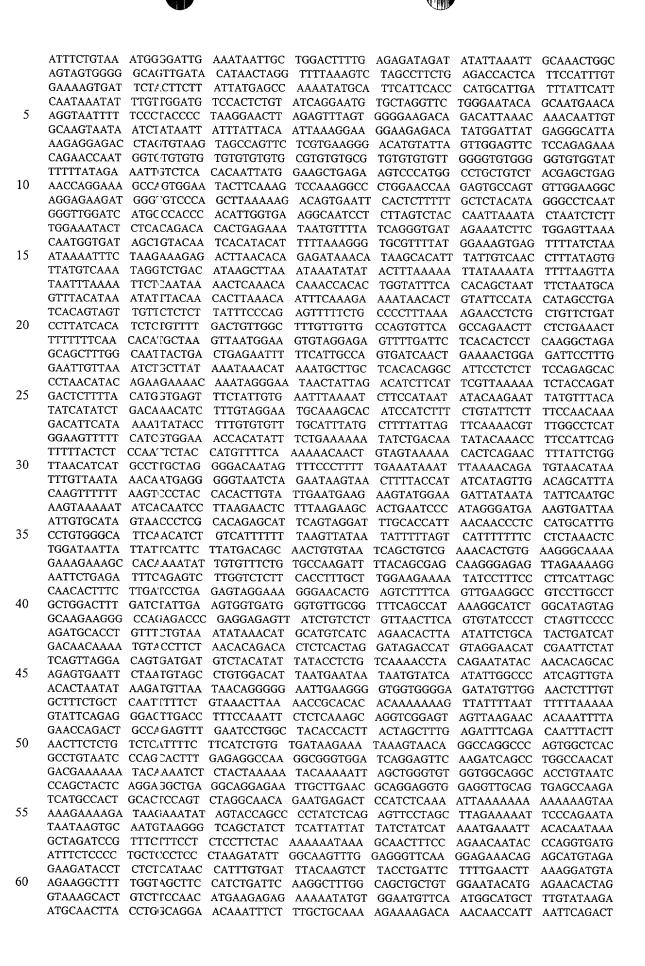
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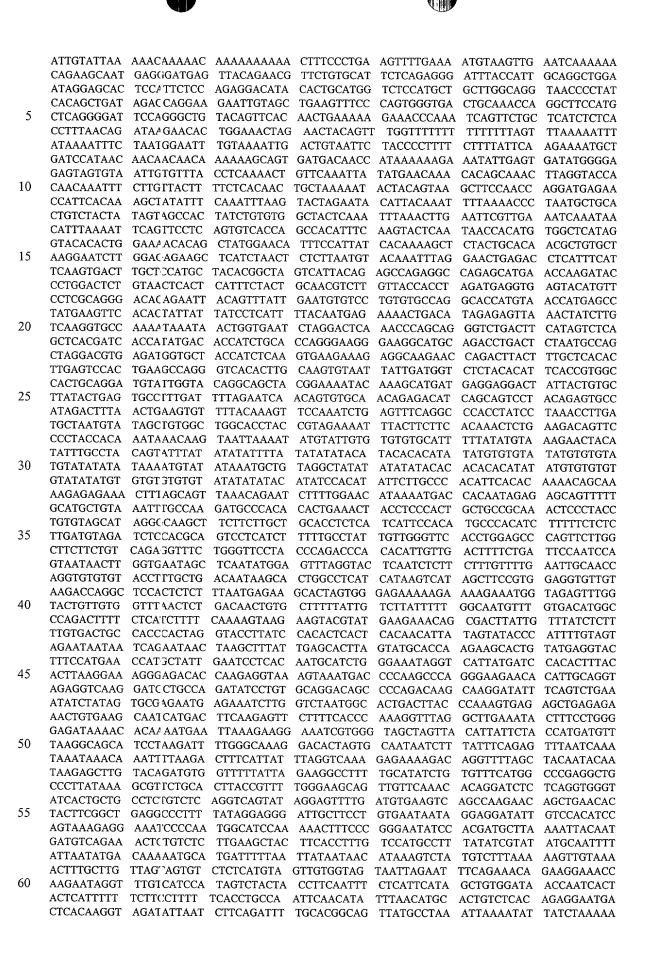
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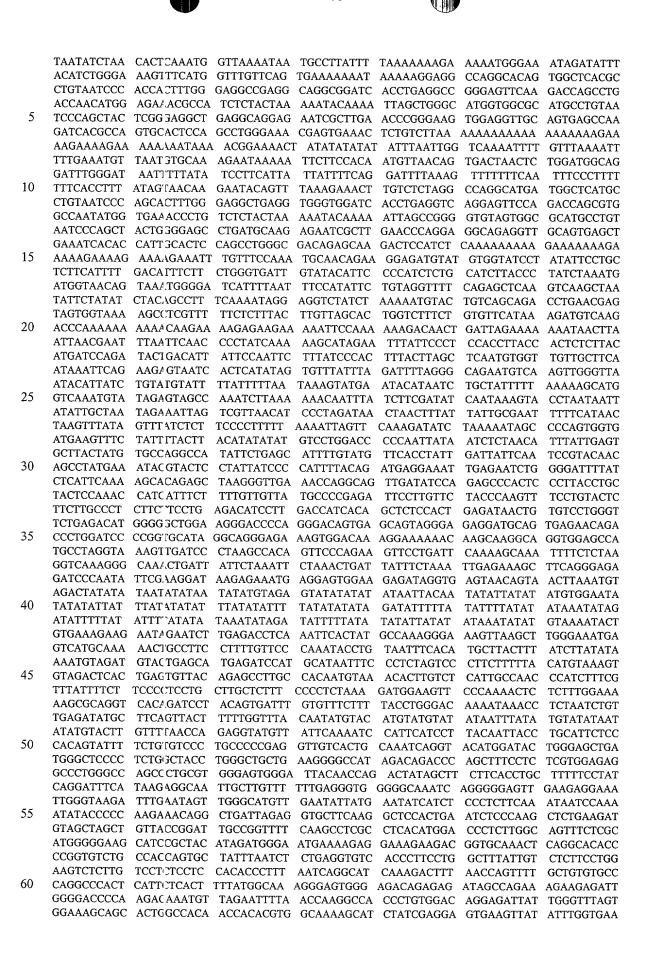


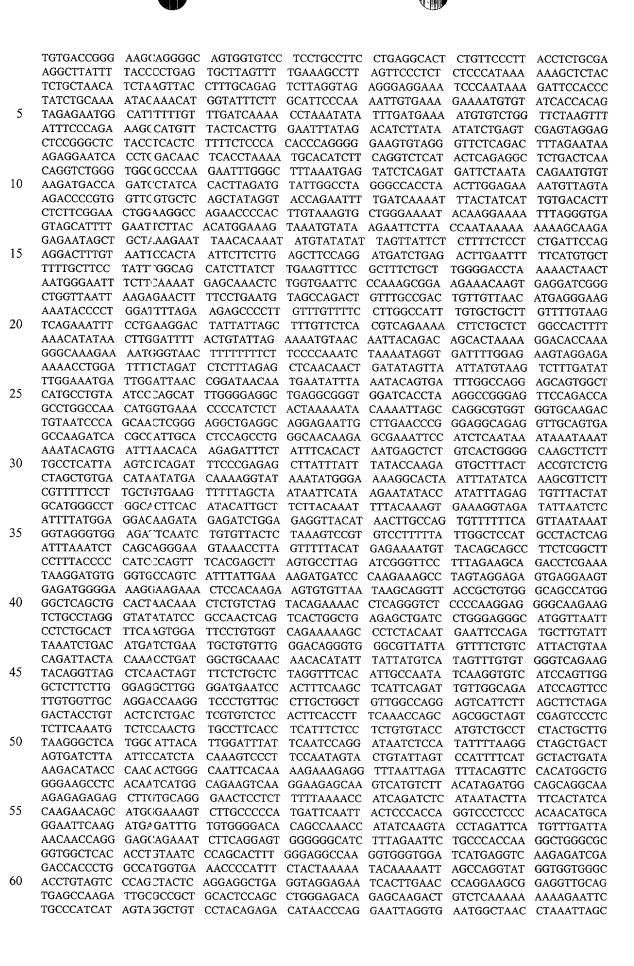
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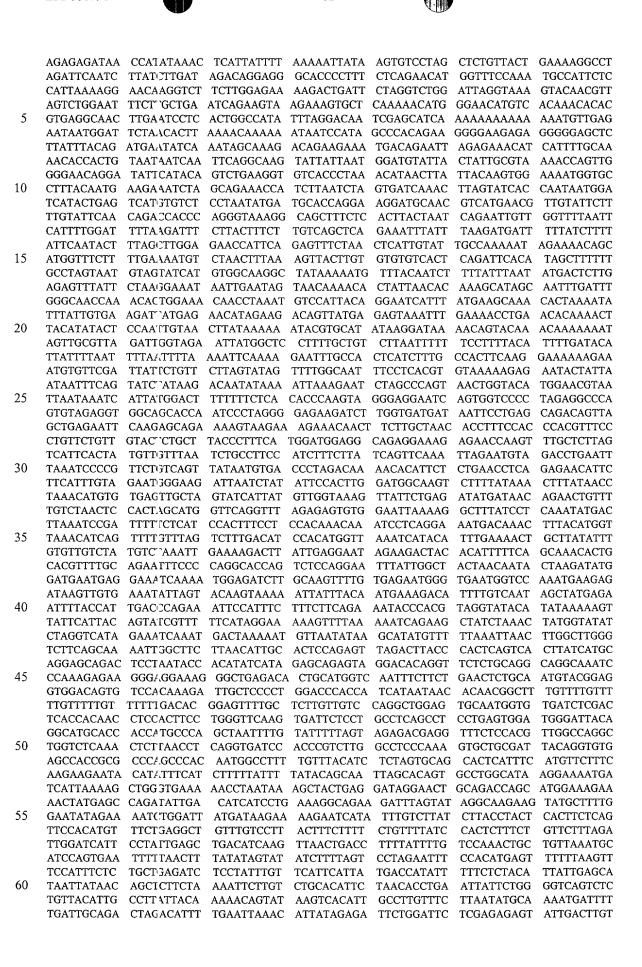


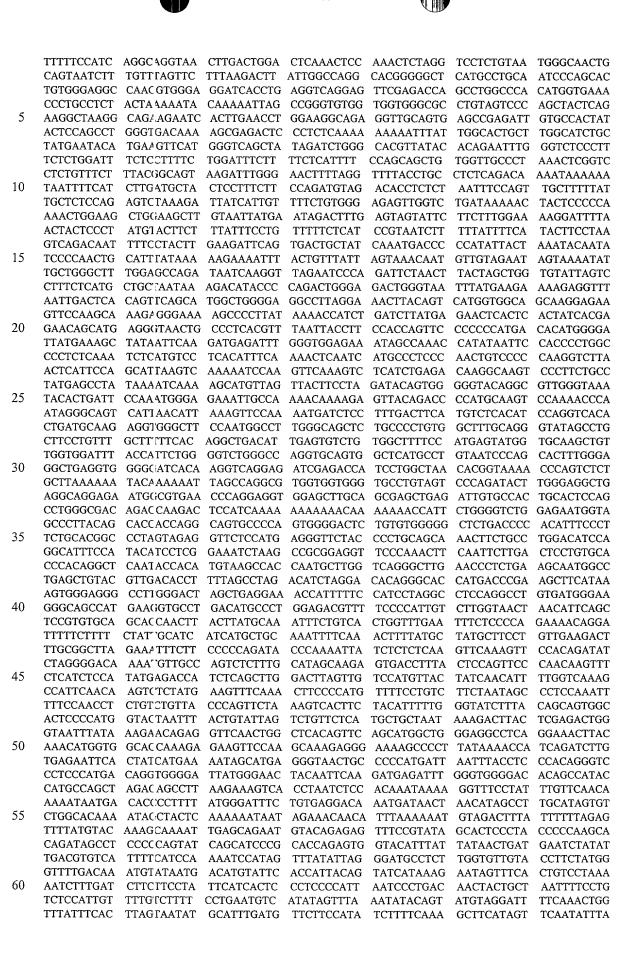


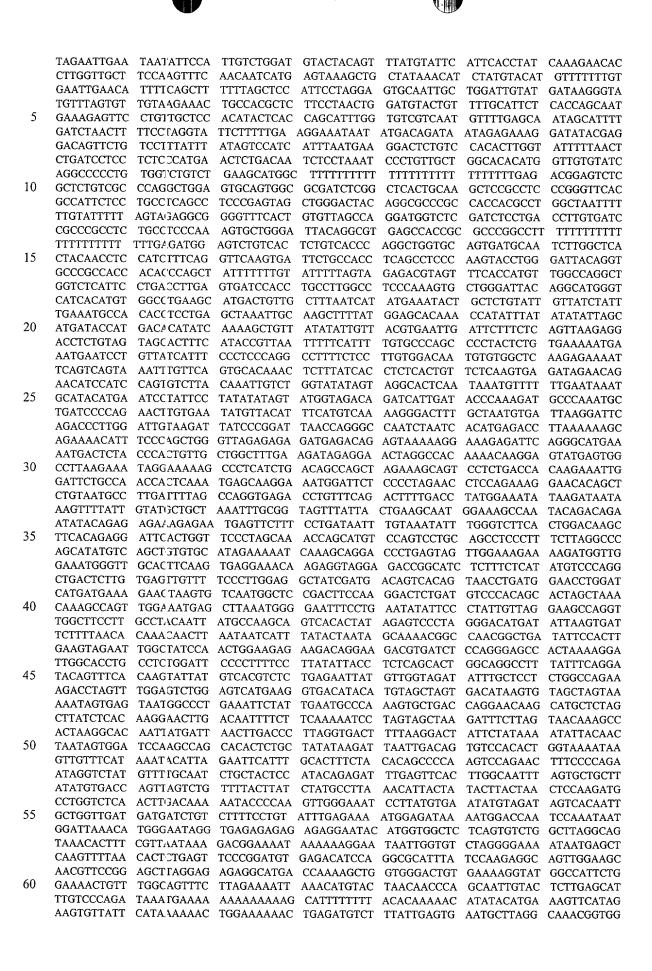




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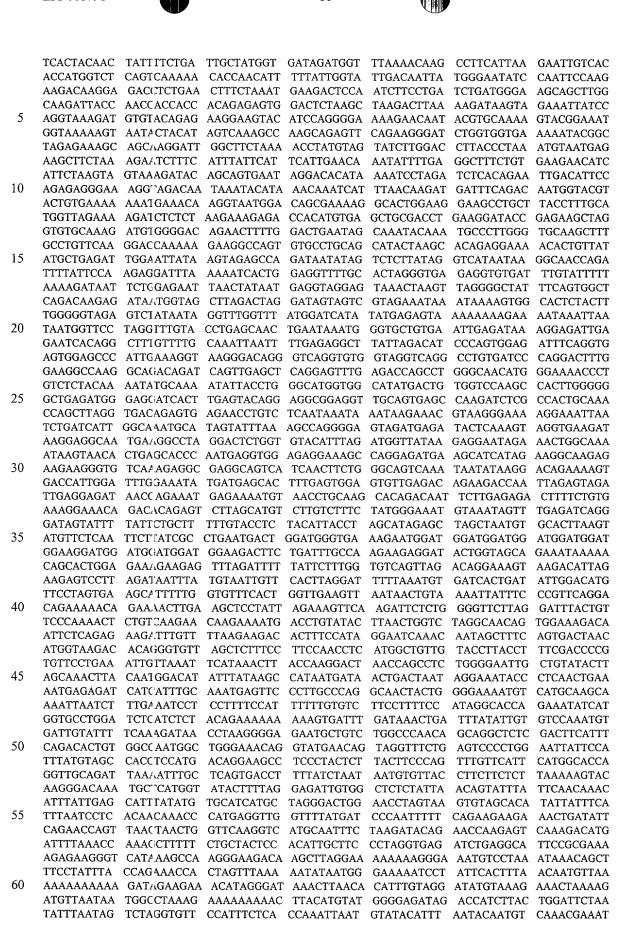


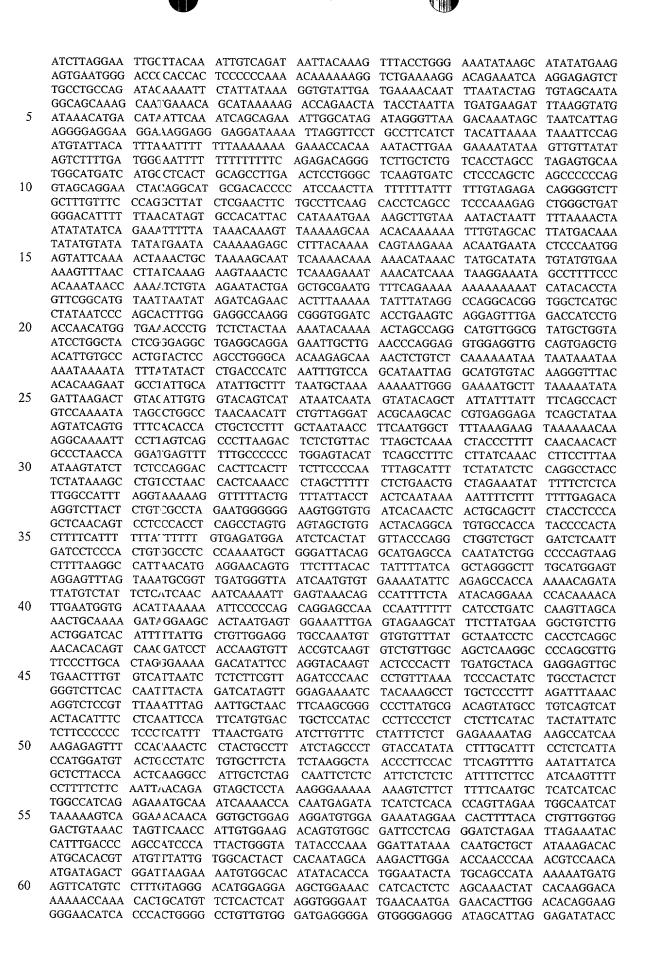




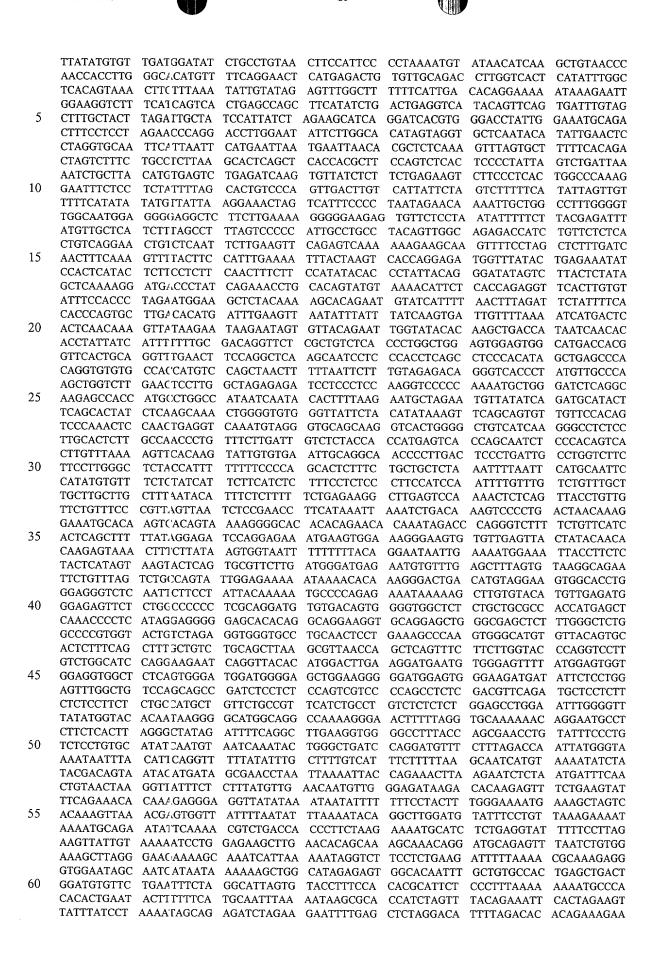


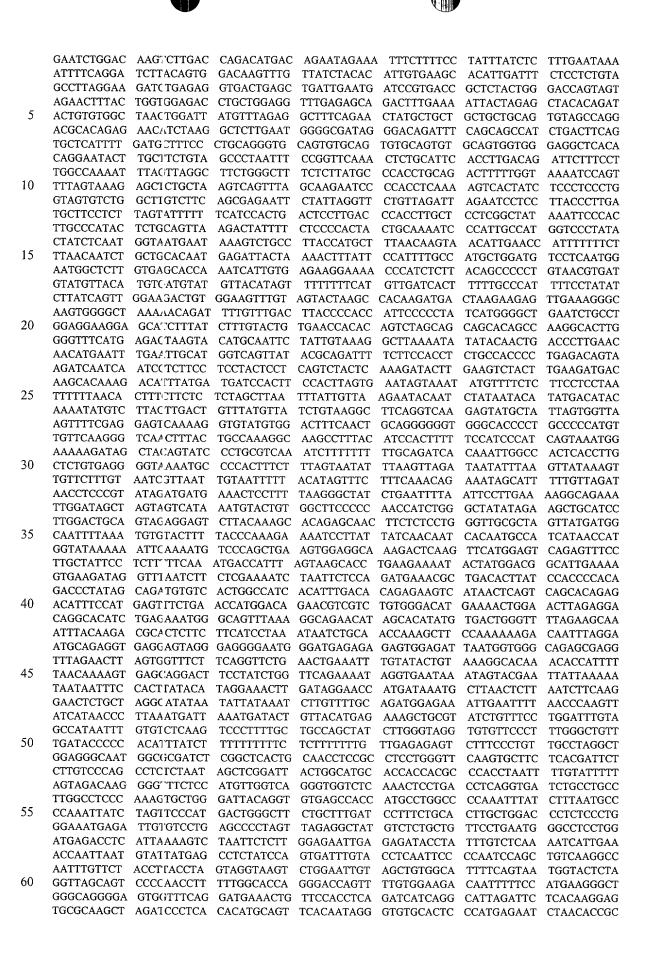
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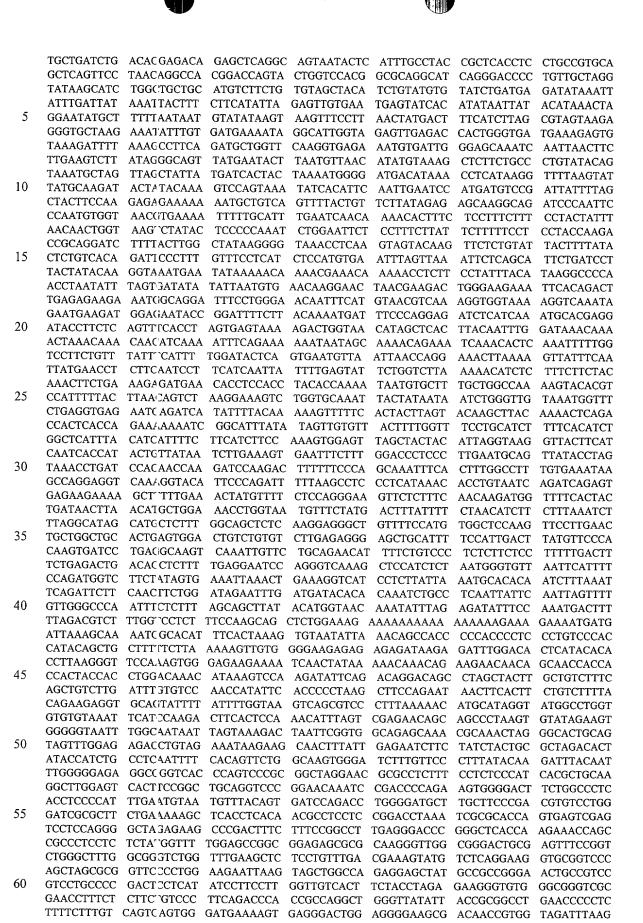


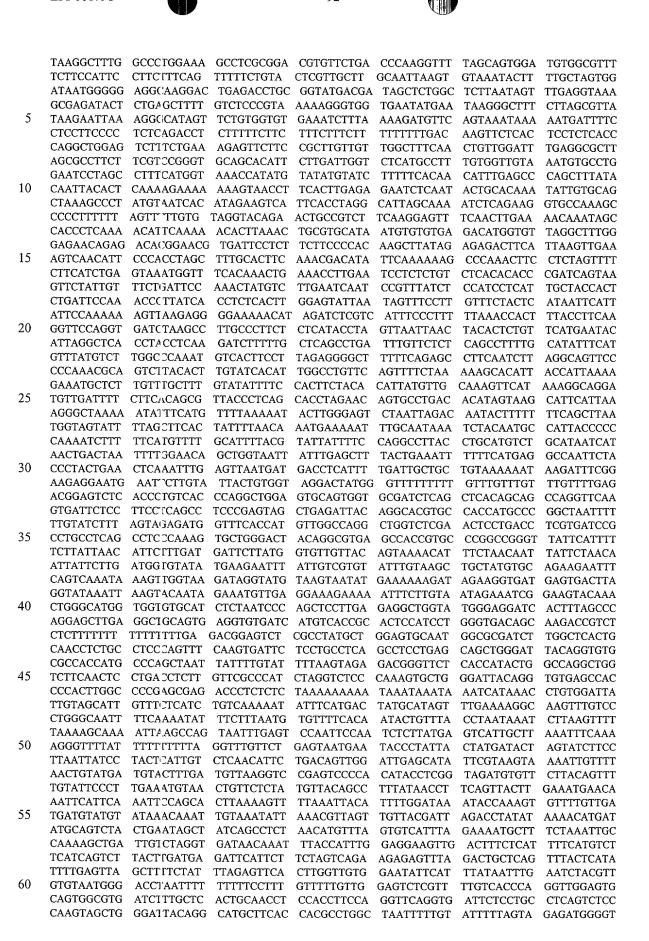






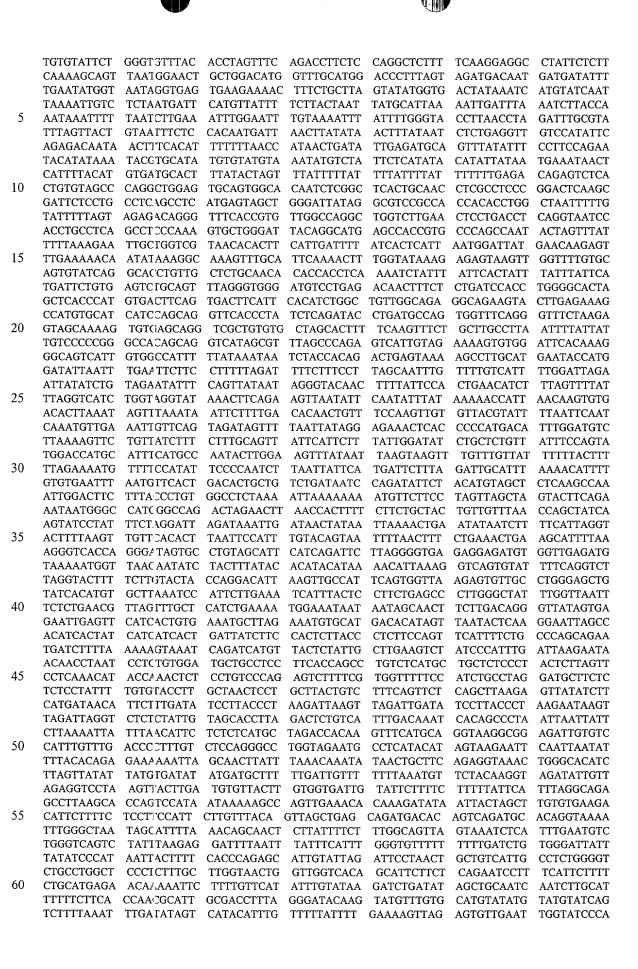


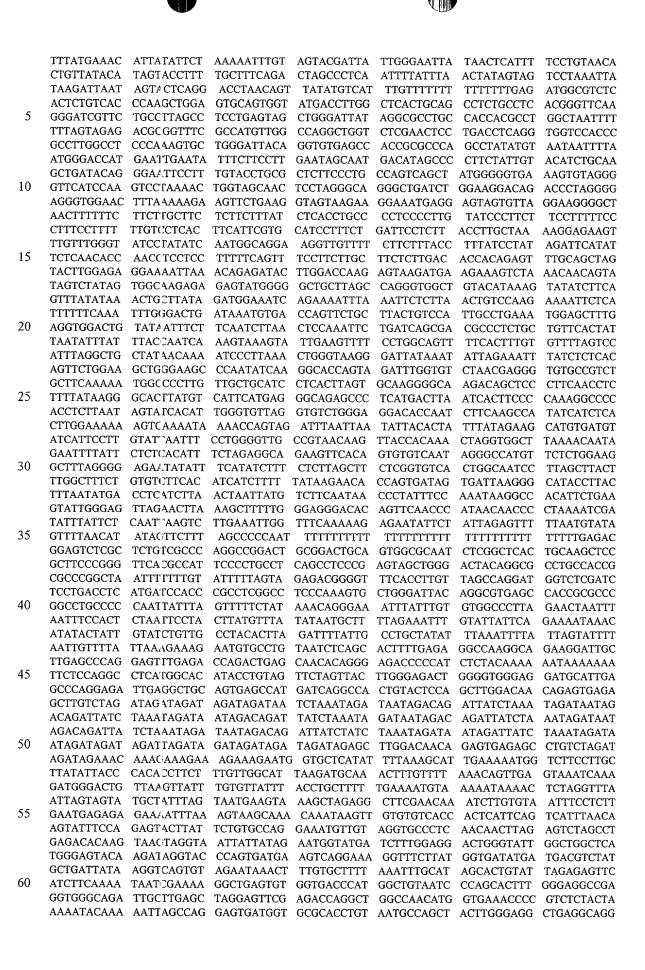


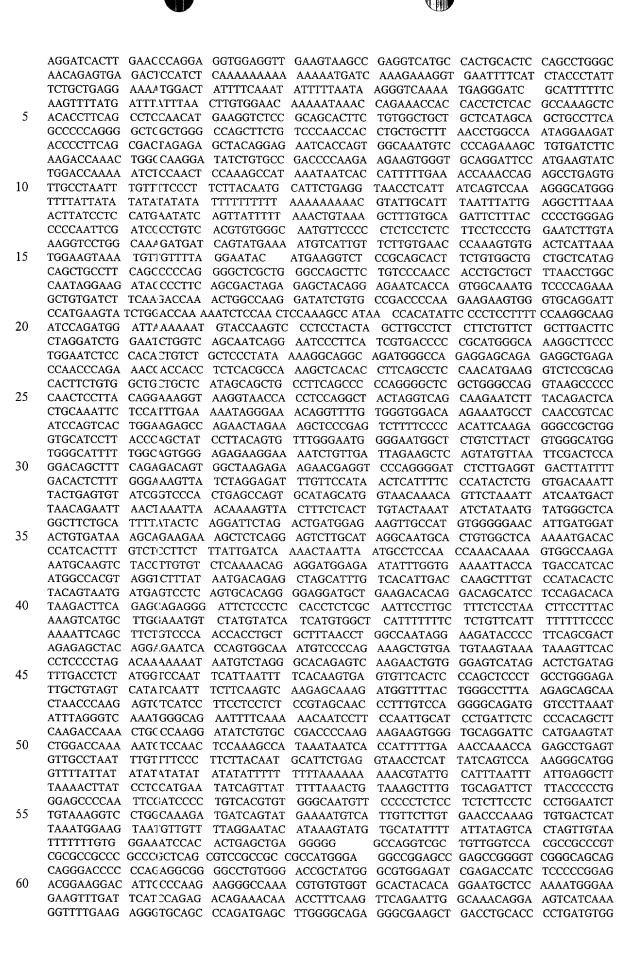


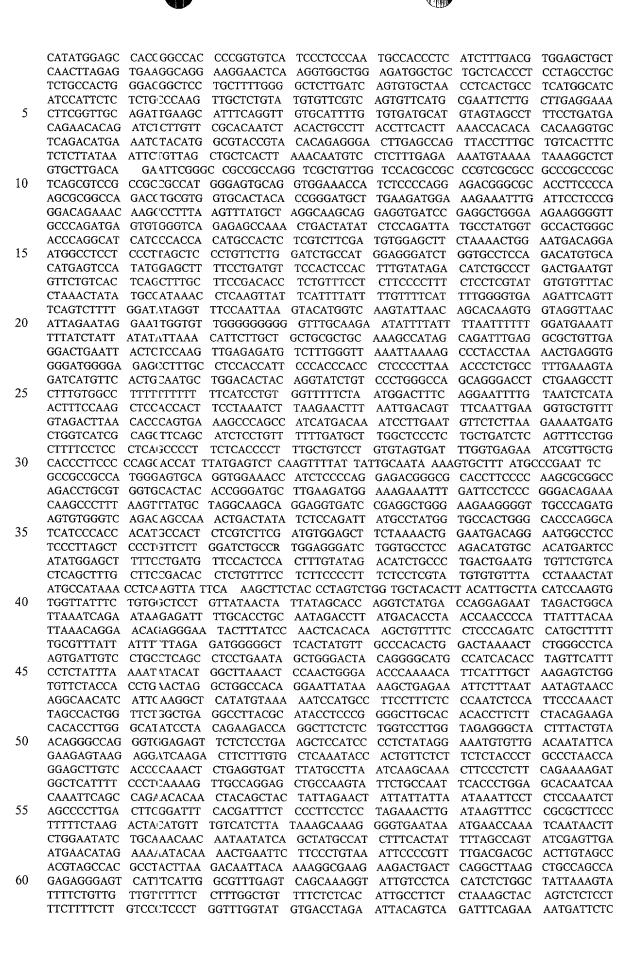


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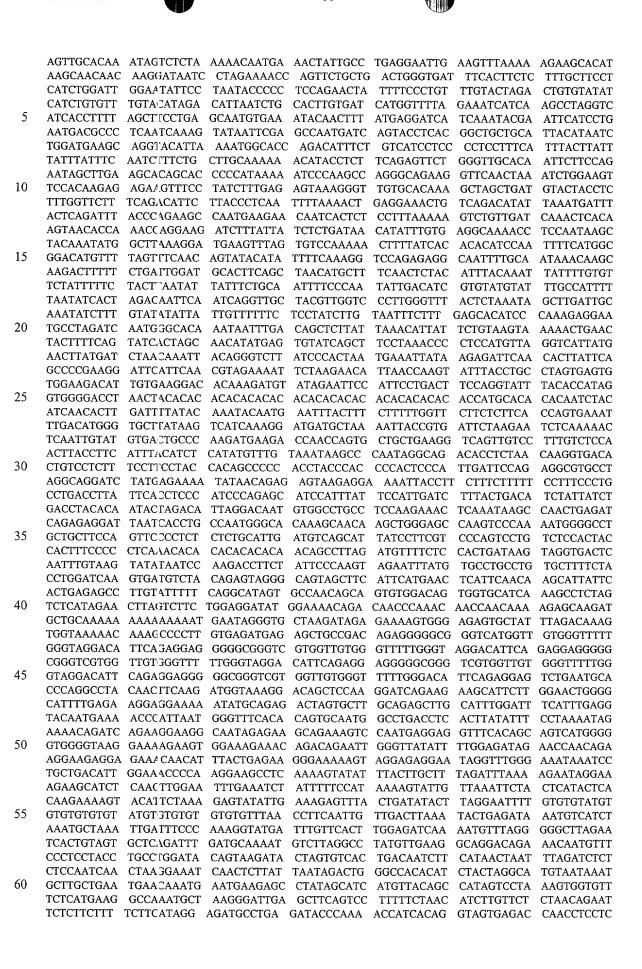












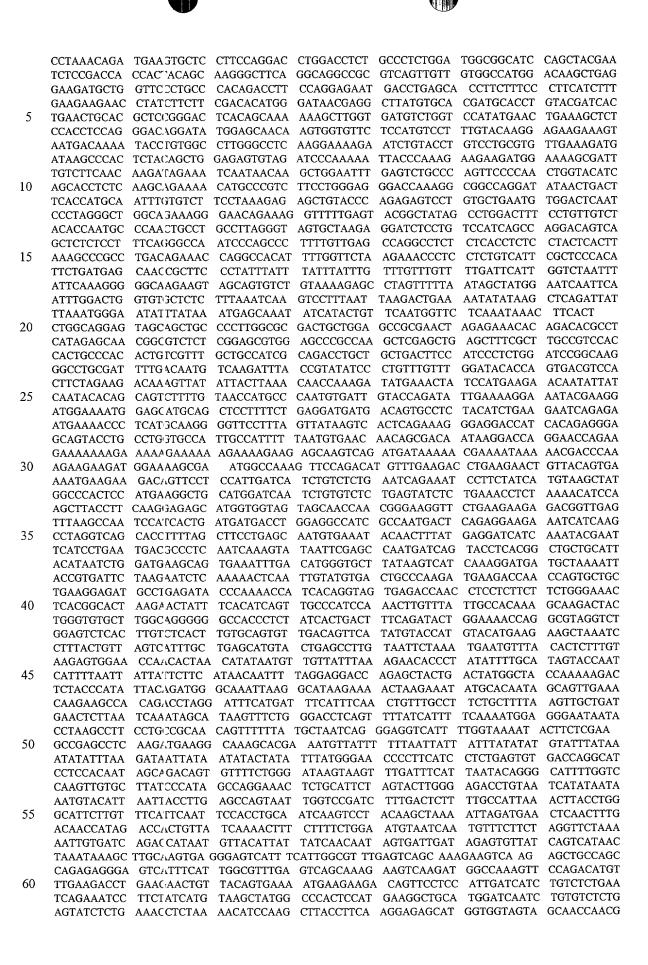


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	TTCAATGGTT	CTGA/ATAAA	CTTCACTGAA	GAAAAAAAA	AAIAIIIAIA	TCCTCATCAT	TCACTCTCTC
50	GATTGACACT	GACAGTAAGC	AAACAGGCTG	TGAGAGTTCT	TGGGACTAAG	CCCACTCCTC	ATTGCTGAGT
	GCTGCAAGTA	CCTAGAAATA	TCCTTGGCCA	CCGAAGACTA	TCCTCCTCAC	CCATCCCCTT	TATTTCCTTC
	TTCAACAGAA	GGATATTCAG	TGCACATCTG	GAACAGGATC	AGCTGAAGCA	CTGCAGGGAG	TCAGGACTGG
	TAGTAACAGC	TACCATGATT	TATCTATCAA	TGCACCAAAC	ATCTGTTGAG	CAAGCGCTAT	GTACTAGGAG
	CTGGGAGTAC	AGAGATGAGA	ACAGTCACAA	GTCCCTCCTC	AGATAGGAGA	GGCAGCTAGT	TATAAGCAGA
55	ACAAGGTAAC	ATGACAAGTA	GAGTAAGATA	GAAGAACGAA	GAGGAGTAGC	CAGGAAGGAG	GGAGGAGAAC
	GACATAAGAA	TCAAGCCTAA	AGGGATAAAC	AGAAGATTTC	CACACATGGG	CTGGGCCAAT	TGGGTGTCGG
	TTACGCCTGT	AATCC CAGCA	CTTTGGGTGG	CAGGGGCAGA	AAGATCGCTT	GAGCCCAGGA	GTTCAAGACC
	AGCCTGGGCA	ACATAGTGAG	ACTCCCATCT	CTACAAAAAA	TAAATAAATA	AATAAAACAA	TCAGCCAGGC
<i>~</i>	ATGCTGGCAT	GCACCTGTAG	TCCTAGCTAC	TTGGGAAGCT	GACACTGGAG	GATTGCTTGA	GCCCAGAAGT
60	TCAAGACTGC	AGTGAGCTTA T	CCGTTGACC TO	GCAGGTCGA C	ACAAACCTTT	TCGAGGCAAA	AGGCAAAAA
	GGCTGCTCTG	GGATT CTCTT	CAGCCAATCT	TCAATGCTCA	AGTGTCTGAA	GCAGCCATGG	CAGAAGTACC
	TAAGCTCGCC	AGTGAAATGA	TGGCTTATTA	CAGTGGCAAT	GAGGATGACT	TGTTCTTTGA	AGCTGATGGC





					CATCACTGAT	GATGACCTGG	AGGCCATCGC
	CAATGACTCA	GAGGAAGAAA	TCATCAAGCC	TAGGTCATCA	CCTTTTAGCT	TCCTGAGCAA	TGTGAAATAC
	AACTTTATGA	<b>GGATCATCAA</b>	ATACGAATTC	ATCCTGAATG	ACGCCCTCAA	TCAAAGTATA	ATTCGAGCCA
	ATGATCAGTA	CCTC ACGGCT	GCTGCATTAC	ATAATCTGGA	TGAAGCAGTG	AAATTTGACA	TGGGTGCTTA
5	TAAGTCATCA	AAGGATGATG	CTAAAATTAC	CGTGATTCTA	AGAATCTCAA	AAACTCAATT	GTATGTGACT
	GCCCAAGATG	AAGACCAACC	AGTGCTGCTG	AAGGAGATGC	CTGAGATACC	CAAAACCATC	ACAGGTAGTG
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	CTTGTTTATT	GCCACAAAGC	AAGACTACTG	GGTGTGCTTG	GCAGGGGGC	CACCCTCTAT	CACTGACTTT
	CAGATACTGG	AAAACCAGGC	GTAGGTCTGG	AGTCTCACTT	GTCTCACTTG	TGCAGTGTTG	ACAGTTCATA
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	GCCCACCCTG	GCCATGAGTG	CGGGGGCACT	GGGAGCTCTA	CAGCTCCCAG	GTGTGCTGAC	AAGGCTGCGA
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4.5	CTCCTGCTGT	CTTCCTCCCG	CTCTCTGATC	TCTGACTCCC	AGAACCTCTC	CCTCTGTCTC	CAGGGCTGCC
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	GTCTCTGTCT	CAGTCTGTCC	TTCACTCTGT	GTGTGTGTGT		CTCTCTCTCC	TTCCCTTCCA
	CTCCCTCTTC	CTCCTGCCTC	CACCTCTCCA	GGCCCCTGTC		GTCCGGCCTT	TCTCTGCCTT
	TCCGTCCTCC				CCAGCCGGAC	CCCCACCCAC	AGTCGGGCCC
					GGAGGGAGGG		ACCTCACCAG
50	CCCCTCTCCG	ACC# CCCCCC	CCTTTCCCTT	TTCAACTTTT	CCAACTTTTC	CTTCCGTGCC	CTCCTCCGAG
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	GGATGTGTCA	GGCCGGCCCT	CCCCTGCCGC	CTGCCCCCCG	CCCGCCCGCC	CCAGGCCCCC	TATATAACCC
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<b>C</b> O					ACGCAGGGAC		
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		~~~~~~					
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		TGGC CGGGTG					ACCCCCGCGC
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_		CCAGGTGCGC					GAGGGCGTCT
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		TCGC GCTCCC					
		CCAC ATTCCG					
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		CGGA.GTCCAG					CCTGGTCCTG
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		GGCC GAGCTG					CGCGGCAGCT
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		GCAC CCACTT					
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		ATTCCCAGCT					
		GCTCTACAGG					
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		AAGACCCTGG					
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25		GCTCTGAGAC					
		TGACCCTGCA					
						ATGACCTCAA	AGTCCCCAGA
		TAAGACCCAA					TCACCTCAAG
• •		CCTGGCCCCA					ACGCCTGTAA
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		CCTGTCTCTA					
		GGCTGAGGCA					
		TCCAGCCTGG					
		AGAAAACCAT					
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	TCACCCCAA	CCCCACACT	CAGCTCTGGA	AGCCCGTCCT	GACTCCAGCC	TCCATTTTCG	GAACCCCACA
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	TTCAGCTGCA	GCTCCACAGC	ACCCCTGCCC	TGCACCCCCG	CTGCACCCCC	TACCTCTCAC	TCACCTCTCT
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00		TACAAAAATG					
		GGCGATTTGT					
	GGAGACCICC	ATTC.AGGTGG	AGGTCCCGAG	CODDDOOD	AGCGACTGGG	AGATGGGTCG	GTCACCCAGA



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TCCTCCCAA AAATAAGCCC TCAGGAGGG ACAAAGTTGA CCGCTGATTG AGCCTGTCAG GGCTGTGCAC-3'
(SEQ. ID NO:3004)

# Human Adenosine A1 Receptor Nucleic Acid and Antisense Oligonucleotide Fragments

5'-ATGCCGCCCT CCATCTCAGC TTTCCAGGCC GCCTACATCG GCATCGAGGT GCTCATCGCC CTGGTCTCTG TGCCCGGGAA CGTCCTGGTG ATCTGGGCGG TGAAGGTGAA CCAGGCGCTG CGGGATGCCA CCTTCTGCTT CATCGTCTCG CTGGCGGTGG CTGATGTGGC CGTGGGTGCC CTGGTCATCC CCCTCGCCAT CCTCATCAAC ATTGGGCCAC AGACCTACTT CCACACCTGC CTCATGGTTG CCTGTCCGGT CCTCATCCTC ACCCAGAGCT CCATCCTGGC CCTGCTGGCA ATTGCTGTGG ACCGCTACCT CCGGGTCAAG ATCCCTCTCC GGTACAAGAT GGTGGTGACC CCCCGGAGGG CGGCGGTGGC CATAGCCGGC TGCTGGATCC TCTCCTTCGT GGTGGGACTG CCCCTATGT TTGGCIGGAA CAATCTGAGT GCGGTGGAGC GGGCCTGGGC AGCCAACGGC AGCATGGGGG AGCCCGTGAT CAACITGCGAG TTCGAGAAGG TCATCAGCAT GGAGTACATG GTCTACTTCA ACTTCTTTGT GTGGGTGCTG CCCCCGCTTC TCCTCATGGT CCTCATCTAC CTGGAGGTCT TCTACCTAAT CCGCAAGCAG CTCAACAAGA AGGTGTCGGC CTCCTCCGGC GACCCGCAGA AGTACTATGG GAAGGAGCTG AAGATCGCCA AGTCGCTGGC CCTC'ATCCTC TTCCTCTTG CCCTCAGCTG GCTGCCTTTG CACATCCTCA ACTGCATCAC CCTCTTCTGC CCGTCCTGCC ACAAGCCCAG CATCCTTACC TACATTGCCA TCTTCCTCAC GCACGGCAAC TCGGCCATGA ACCCCATTGT CTATGCCTTC CGCATCCAGA AGTTCCGCGT CACCTTCCTT AAGATTTGGA ATGACCATTT CCGCTGCCAG CCTGCACCTC CCATTGACGA GGATCTCCCA GAAGAGAGGC CTGATGACTA G ATGAGTGTCA GAAGTGTGAA GGGTGCCTGT TCTGAATCCC AGAGCCTCCT CTCCCTCTGT GAGGCTGGCA GGTGAGGAAG GGT1TAACCT CACTGGAAGG AATCCCTGGA GCTAGCGGCT GCTGAAGGCG TCGAGGTGTG GGGGCACTTG GACAGAACAG TCAGGCAGCC GGGAGCTCTG CCAGCTTTGG TGACCTTGGG CCGGGCTGGG CGCGGCCCGG AGCTCTGTTC CCTGGAACTT TGGGCACTGC CTCTGGGACC CCTGCCGGCC AGCAGGCAGG ATGGTGCTTG CCTCGTGCCC CTTGGTGCCC GTCTGCTGAT GTGCCCAGCC TGTGCCCGCC ATGCCGCCCT CCATCTCAGC TTTCCAGGCC GCCTACATCG GCATCGAGGT GCTCATCGCC CTGGTCTCTG TGCCCGGGAA CGTGCTGGTG ATCTGGGCGG TGAAGGTGAA CCAGGCGCTG CGGGATGCCA CCTTCTGCTT CATCGTGTCG CTGGCGGTGG CTGATGGC CGTGGGTGCC CTGGTCATCC CCCTCGCCAT CCTCATCAAC ATTGGGCCAC AGACCTACTT CCACACCTGC CTCATGGTTG CCTGTCCGGT CCTCATCCTC ACCCAGAGCT CCATCCTGGC CCTGCTGGCA ATTGCTGTGG ACCGCTACCT CCGGGTCAAG ATCCCTCTCC GGTACAAGAT GGTGGTGACC CCCCGGAGGG CGGCGGTGGC CATAGCCGGC TGCTGGATCC TCTCCTTCGT GGTGGGACTG ACCCCTATGT TTGGCTGGAA CAATCTGAGT GCGGTGGAGC GGGCCTGGGC AGCCAACGGC AGCATGGGGG AGCCCGTGAT CAAGTGCGAG TTCCAGAAGG TCATCAGCAT GGAGTACATG GTCTACTTCA ACTTCTTTGT GTGGGTGCTG CCCCCGCTTC TCCTCATGGT CCTCATCTAC CTGGAGGTCT TCTACCTAAT CCGCAAGCAG CTCAACAAGA AGGTGTCGGC CTCCTCCGGC GACCCGCAGA AGTACTATGG GAAGGAGCTG AAGATCGCCA AGTCGCTGGC CCTCATCCTC TTCCTCTTG CCCTCAGCTG GCTGCCTTTG CACATCCTCA ACTGCATCAC CCTCTTCTGC CCGTCCTGCC ACAGCCCAG CATCCTTACC TACATTGCCA TCTTCCTCAC GCACGGCAAC TCGGCCATGA ACCCCATTGT CTATGCCTTC CGCATCCAGA AGTTCCGCGT CACCTTCCTT AAGATTTGGA ATGACCATTT CCGCTGCCAG CCTGCACCTC CCATTGACGA GGATCTCCCA GAAGAGAGGC CTGATGACTA GACCCCGCCT TCCGCTCCCA CCAGCCCACA TCCAGTGGGG TCTCAGTCCA GTCCTCACAT GCCCGCTGTC CCAGGGGTCT CCCTGAGCCT GCCCCAGCTG GGCTGTTGGC TGGGGGCATG GGGGAGGCTC TGAAGAGATA CCCACAGAGT GTGGTCCCTC CACTAGGAGT TAACTACCCT ACACCTCTGG GCCCTGCAGG AGGCCTGGGA GGGCAAGGGT CCTACGGAGG GACCAGGTGT CTAGAGGCAA CAGTGTTCTG AGCCCCCACC TGCCTGACCA TCCCATGAGC AGTCCAGCGC TTCAGGGCTG GGCAGGTCCT GGGGAGGCTG AGACTGCAGA GGAGCCACCT GGGCTGGGAG AAGGTGCTTG GGCTTCTGCG GTGAGGCAGG GGAGTCTGCT TGTCTTAGAT GTTGGTGGTG CAGCCCCAGG ACCAAGCTTA AGGAGAGGAG AGCATCTGCT CTGAGACGGA TGGAAGGAGA GAGGTTGAGG ATGCACTGGC CTGTTCTGTA GGAGAGACTG GCCAGAGGCA GCTAAGGGGC AGGAATCAAG GAGCCTCCGT TCCCACCTCT GAGGACTCTG GACCCCAGGC CATACCAGGT GCTAGGGTGC CTGCTCTCCT TGCCCTGGGC CAGCCCAGGA



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			CTGTAGGCGC				
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			GCGG C GBT GGI				
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			GGTGGGACTG				
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			AAGATTTGGA				
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	CGGGATGCCA	CCTTCTGCTT	CATCGTGTCG	CTGGCGGTGG	CTGATGTGGC	CGTGGGTGCC	CTGGTCATCC
	CCCTCGCCAT	CCTC ATCAAC	ATTGGGCCAC	AGACCTACTT	CCACACCTGC	CTCATGGTTG	CCTGTCCGGT
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15	GAAGAGAGGC	CTGATGACTA			CCAGCCCACA		TCTCAGTCCA
			CCAGGGGTCT			GGCTGTTGGC	TGGGGGCATG
	GGGGAGGCTC				CACTAGGAGT		ACACCTCTGG
						CTAGAGGCAA	
20	AGCCCCCACC					GGCAGGTCCT	
20						GTGAGGCAGG	
	TGTCTTAGAT		CAGCCCCAGG			AGCATCTGCT	
	TGGAAGGAGA	GAGGTTGAGG	ATGCACTGGC	CTGTTCTGTA	GGAGAGACTG	GCCAGAGGCA	GCTAAGGGGC
	AGGAATCAAG	GAGCCTCCGT	TCCCACCTCT	GAGGACTCTG	GACCCCAGGC	CATACCAGGT	GCTAGGGTGC
	CTGCTCTCCT	TGCCCTGGGC	CAGCCCAGGA	TTGTACGTGG	GAGAGGCAGA	AAGGGTAGGT	TCAGTAATCA
25	TTTCTGATGA	TTTGCTGGAG	TGCTGGCTCC	ACGCCCTGGG	GAGTGAGCTT	GGTGCGGTAG	GTGCTGGCCT
	CAAACAGCCA	CGAGGTGGTA				TCCGGGGAGG	AGCCTGGAGT
	GTAATTACCT		CCACCAGCTC			CCTGGACTGT	CCTAGGTGAC
	CCCATCTCTG				CTAGACATGC		GCATTCTGCC
		CGGGGTGGAC					CCCTGGGGTG
30	GGTTTAGCAG					TGGGGGAAGG	
	ATGTGAATCC	CTCAATACCC	CTAGTATCTG	GCTGGGTTTT	CAGGGGCTTT	GGAAGCTCTG	TTGCAGGTGT
	CCGGGGGTCT		GGATCTGGGA			TGCCCTGCCA	
						GCGAGGCGGG	
25						GGGCGAGGGA	
35	CCGTCGGTTG	ACCITCTGAA	CATGAGTGTC		CTTGCTTCCA		TCTGTTGGAA
	ATTGGGTGTG	CCCIGGCTCC	CAAGGGAGGC	CCATGTGACT	AATAAAAAAC		CGCATTTGTG
		AGA ATCTGGA					AAATCCTTAG
	ATTCAAGCAG	AAG AATTCCA					TTTTTGTTTT
	TTTGTTTTTT	TGTT TTTTT	<b>FGAGATGGAG</b>	TCTCGCTGTG	TTACCGGGAG	CGACAGAGCC	GCACGGCCGA
40	GTCGAGTCCC	AGCCAGCTAC	CATCCCTCTG	GAGCTTACCG	GCCGGCCTTG	GCTTCCCCAG	GAATCCCTGG
	AGCTAGCGGC	TGC1GAAGGC	GTCGAGGTGT	GGGGGCACTT	GGACAGAACA	GTCAGGCAGC	CGGGAGCTCT
	GCCAGCTTTG	GTGACCTTGG	GTGCTTGCCT	CGTGCCCCTT	GGTGCCCGTC	TGCTGATGTG	CCCAGCCTGT
	GCCCGCCATG	CCGCCCTCCA	TCTCAGCTTT	CCAGGCCGCC	TACATCGGCA	TCGAGGTGCT	CATCGCCCTG
						GGCGCTGCGG	
45						GTCATCCCCC	TCGCCATCCT
						GTCCGGTCCT	
						GGTCAAGATC	
						TGGATCCTCT	
50						CCTGGGCAGC	
50						GTACATGGTC	
						GAGGTCTTCT	
						ACTATGGGAA	
	ATCGCCAAGT					GCCTTTGCAC	
						ATTGCCATCT	
55	CGGCAACTCG	GCCATGAACC	CCATTGTCTA	TGCCTTCCGC	ATCCAGAAGT	TCCGCGTCAC	CTTCCTTAAG
	ATTTGGAATG	ACCATTTCCG	CTGCCAGCCT	GCACCTCCCA	TTGACGAGGA	TCTCCCAGAA	GAGAGGCCTG
							TCACATGCCC
						GGCATGGGGG	
						CTCTGGGCCC	
60						GTTCTGAGCC	
						AGGCTGAGAC	
						TCTGCTTGTC	
						1010011010	



GTGGTGCAGC CCCAGGACCA AGCTTAAGGA GAGGAGAGCA TCTGCTCTGA GACGGATGGA AGGAGAGAGG TTGAGGATGC ACTGGCCTGT TCTGTAGGAG AGACTGGCCA GA -3'(FRAG.NO: )(SEO.NO:3005) [2423]] 5'-CGCATTTGTG TT1TAATAAA AGAATCTGGA AGATAAATAG TCTTGAAGAG AGACAAAGGA AGGAAAATTT AAATCCTTAG ATTC'AAGCAG AAGAATTCCA TGTGGAAGGT TTGGGTTGTT GTTGTTGTTG TTTGGTGTGT TTTTTGTTTT TTTGTTTTTT TGAGATGGAG TCTCGCTGTG TTACCGGGAG CGACAGAGCC GCACGGCCGA GTCGAGTCCC AGCCAGCTAC CATCCCTCTG GAGCTTACCG GCCGGCCTTG GCTTCCCCAG GAATCCCTGG AGCIAGCGC TGCTGAAGGC GTCGAGGTGT GGGGGCACTT GGACAGAACA GTCAGGCAGC CGGGAGCTCT GCCAGCTTTG GTGACCTTGG GTGCTTGCCT CGTGCCCCTT GGTGCCCGTC TGCTGATGTG CCCAGCCTGT GCCCGCCATG CCGCCCTCCA TCTCAGCTTT CCAGGCCGCC TACATCGGCA TCGAGGTGCT CATCGCCCTG GTCTCTGTGC CCGGGAACGT GCTGGTGATC TGGGCGGTGA AGGTGAACCA GGCGCTGCGG GATGCCACCT TCTCCTTCAT CGTGTCGCTG GCGGTGGCTG ATGTGGCCGT GGGTGCCCTG GTCATCCCCC TCGCCATCCT CATCAACATT GGGCCACAGA CCTACTTCCA CACCTGCCTC ATGGTTGCCT GTCCGGTCCT CATCCTCACC CAGAGCTCCA TCCTGGCCCT GCTGGCAATT GCTGTGGACC GCTACCTCCG GGTCAAGATC CCTCTCCGGT ACAAGATGGT GGTGACCCCC CGGAGGGCGG CGGTGGCCAT AGCCGGCTGC TGGATCCTCT CCTTCGTGGT GGGACTGACC CCTATGTTTG GCTGGAACAA TCTGAGTGCG GTGGAGCGGG CCTGGGCAGC CAACGGCAGC ATGGGGGAGC CCGTGATCAA GTGCGAGTTC GAGAAGGTCA TCAGCATGGA GTACATGGTC TACTTCAACT TCTTTGTGTG GGTGCTGCCC CCGCTTCTCC TCATGGTCCT CATCTACCTG GAGGTCTTCT ACCTAATCCG CAACCAGCTC AACAAGAAGG TGTCGGCCTC CTCCGGCGAC CCGCAGAAGT ACTATGGGAA GGAGCTGAAG ATCIJCCAAGT CGCTGGCCCT CATCCTCTTC CTCTTTGCCC TCAGCTGGCT GCCTTTGCAC ATCCTCAACT GCATCACCCT CTTCTGCCG TCCTGCCACA AGCCCAGCAT CCTTACCTAC ATTGCCATCT TCCTCACGCA CGGC'AACTCG GCCATGAACC CCATTGTCTA TGCCTTCCGC ATCCAGAAGT TCCGCGTCAC CTTCCTTAAG ATTT3GAATG ACCATTTCCG CTGCCAGCCT GCACCTCCCA TTGACGAGGA TCTCCCAGAA TCACATGCCC GCTGTCCCAG GGGTCTCCCT GAGCCTGCCC CAGCTGGGCT GTTGGCTGGG GGCATGGGGG AGGCTCTGAA GAGATACCCA CAGAGTGTGG TCCCTCCACT AGGAGTTAAC TACCCTACAC CTCTGGGCCC TGCAGGAGGC CTGCGAGGGC AAGGGTCCTA CGGAGGGACC AGGTGTCTAG AGGCAACAGT GTTCTGAGCC CCCACCTGCC TGACCATCCC ATGAGCAGTC CAGAGCTTCA GGGCTGGGCA GGTCCTGGGG AGGCTGAGAC TGCAGAGGAG CCACCTGGGC TGGGAGAAGG TGCTTGGGCT TCTGCGGTGA GGCAGGGGAG TCTGCTTGTC TTAGATGTTG GTGGTGCAGC CCCAGGACCA AGCTTAAGGA GAGGAGAGCA TCTGCTCTGA GACGGATGGA AGGAGAGAGG TTGA 3GATGC ACTGGCCTGT TCTGTAGGAG AGACTGGCCA GA -3' (FRAG. NO: )(SEQ. ID NO: 2434) 5'- ATGAGTGTCA GAAGTGTGAA GGGTGCCTGT TCTGAATCCC AGAGCCTCCT CTCCCTCTGT GAGGCTGGCA GGTGAGGAAG GGTTAAACCT CACTGGAAGG AATCCCTGGA GCTAGCGGCT GCTGAAGGCG TCGAGGTGTG GGGGCACTTG GACAGAACAG TCAGGCAGCC GGGAGCTCTG CCAGCTTTGG TGACCTTGGG CCGGGCTGGG CGCGGCCCGG AGC1'CTGTTC CCTGGAACTT TGGGCACTGC CTCTGGGACC CCTGCCGGCC AGCAGGCAGG ATGGTGCTTG CCTCGTGCCC CTTGGTGCCC GTCTGCTGAT GTGCCCAGCC TGTGCCCGCC ATGCCGCCCT CCATCTCAGC TTTCCAGGCC GCCTACATCG GCATCGAGGT GCTCATCGCC CTGGTCTCTG TGCCCGGGAA CGTGCTGGTG ATCTGGGCGG TGAAGGTGAA CCAGGCGCTG CGGGATGCCA CCTTCTGCTT CATCGTGTCG CTGGCGGTGG CTGATGTGC CGTGGGTGCC CTGGTCATCC CCCTCGCCAT CCTCATCAAC ATTGGGCCAC AGACCTACTT CCAC'ACCTGC CTCATGGTTG CCTGTCCGGT CCTCATCCTC ACCCAGAGCT CCATCCTGGC CCTGCTGGCA ATTGCTGTGG ACCGCTACCT CCGGGTCAAG ATCCCTCTCC GGTACAAGAT GGTGGTGACC CCCCGGAGGG CGGCGGTGGC CATAGCCGGC TGCTGGATCC TCTCCTTCGT GGTGGGACTG ACCCCTATGT TTGGCTGGAA CAATCTGAGT GCGGTGGAGC GGGCCTGGGC AGCCAACGGC AGCATGGGGG AGCCCGTGAT CAAGTGCGAG TTCCAGAAGG TCATCAGCAT GGAGTACATG GTCTACTTCA ACTTCTTTGT GTGGGTGCTG CCCCCGCTTC TCCTCATGGT CCTCATCTAC CTGGAGGTCT TCTACCTAAT CCGCAAGCAG CTCAACAAGA AGGTGTCGGC CTCCTCCGGC GACCCGCAGA AGTACTATGG GAAGGAGCTG AAGATCGCCA AGTCGCTGGC CCTCATCCTC TTCCTCTTTG CCCTCAGCTG GCTGCCTTTG CACATCCTCA ACTGCATCAC CCTCTTCTGC CCGTCCTGCC ACAAGCCCAG CATCCTTACC TACATTGCCA TCTTCCTCAC GCACGGCAAC TCGGCCATGA ACCCCATTGT CTATGCCTTC CGCATCCAGA AGTTCCGCGT CACCTTCCTT AAGATTTGGA ATGACCATTT CCGCTGCCAG CCTGCACCTC CCATTGACGA GGATCTCCCA GAAGAGAGGC CTGATGACTA GACCCCGCCT TCCGCTCCCA CCAGCCCACA TCCAGTGGGG TCTCAGTCCA GTCCTCACAT GCCCGCTGTC CCAGGGGTCT CCCTGAGCCT GCCCCAGCTG GGCTGTTGGC TGGGGGGCATG GGGGAGGCTC TGAAGAGATA CCCACAGAGT GTGGTCCCTC CACTAGGAGT TAACTACCCT ACACCTCTGG GCCCTGCAGG AGGCCTGGGA GGGCAAGGGT CCTACGGAGG GACCAGGTGT CTAGAGGCAA CAGTGTTCTG AGCCCCCACC TGCCTGACCA TCCCATGAGC AGTCCAGCGC TTCAGGGCTG GGCAGGTCCT GGGGAGGCTG AGACTGCAGA GGAGCCACCT GGGCTGGGAG AAGGTGCTTG GGCTTCTGCG GTGAGGCAGG GGAGTCTGCT TGTCTTAGAT GTTGGTGGTG CAGCCCCAGG ACCAAGCTTA AGGAGAGGAG AGCATCTGCT CTGAGACGGA TGGAAGGAGA GAGGTTGAGG ATGCACTGGC CTGTTCTGTA GGAGAGACTG GCCAGAGGCA GCTAAGGGGC AGGAATCAAG GAGCCTCCGT TCCCACCTCT GAGGACTCTG GACCCCAGGC CATACCAGGT GCTAGGGTGC CTGCTCTCCT TGCCCTGGGC CAGCCCAGGA TTGTACGTGG GAGAGGCAGA AAGGGTAGGT TCAGTAATCA TTTCTGATGA TTTGCTGGAG TGCTGGCTCC ACGCCCTGGG GAGTGAGCTT GGTGCGGTAG GTGCTGGCCT CAAACAGCCA CGAGGTGGTA GCTCTGAGCC



	CTCCTTCTTG	CCCTGAGCTT	TCCGGGGAGG	AGCCTGGAGT	GTAATTACCT	GTCATCTGGG	CCACCAGCTC
						CTGCTTCTGG	
	GAGGAGAACA	CTAGACATGC	CAACTCGGGA	GCATTCTGCC	TGCCTGGGAA	CGGGGTGGAC	GAGGGAGTGT
	CTGTAAGGAC	TCACTGTTGA	CTGTAGGCGC	CCCTGGGGTG	GGTTTAGCAG	GCTGCAGCAG	GCAGAGGAGG
5						CTCAATACCC	
	GCTGGGTTTT	CAGC GGCTTT	GGAAGCTCTG	TTGCAGGTGT	CCGGGGGTCT	AGGACTTTAG	GGATCTGGGA
						GGGGCAAGG	
	TGGAGCCCCT	GTGTGGGAGG	GCGAGGCGGG	GGAGCCTGGA	GCCCCTGTGT	GGGAGGGCGA	GGCGGGGGAT
						ACCTTCTGAA	
10						CCCTGGCTCC	
	CCATGTGACT A	AATAAAAAC T	GTGAACCCT -3'	(FRAG. NO:_	)(SEQ. ID NO	: 2433)	
	5'- ATGCCGCC	CT CCATCTCAC	GC TTTCCAGGC	C GCCTACATCO	G GCATCGAGGT	GCTĆATCGCC	CTGGTCTCTG
	TGCCCGGGAA	CGTGCTGGTG	ATCTGGGCGG	TGAAGGTGAA	CCAGGCGCTG	CGGGATGCCA	CCTTCTGCTT
	CATCGTCTCG	CTGC CGGTGG	CTGATGTGGC	CGTGGGTGCC	CTGGTCATCC	CCCTCGCCAT	CCTCATCAAC
15	ATTGGGCCAC	AGACCTACTT		CTCATGGTTG		CCTCATCCTC	
	CCATCCTGGC	CCTG CTGGCA	ATTGCTGTGG	ACCGCTACCT	CCGGGTCAAG	ATCCCTCTCC	GGTACAAGAT
	GGTGGTGACC	CCCC'GGAGGG				TCTCCTTCGT	
	ACCCCTATGT	TTGGCTGGAA	CAATCTGAGT	GCGGTGGAGC	GGGCCTGGGC	AGCCAACGGC	AGCATGGGGG
	AGCCCGTGAT	CAAGTGCGAG	TTCGAGAAGG	TCATCAGCAT	GGAGTACATG	GTCTACTTCA	ACTTCTTTGT
20				CCTCATCTAC			
	CTCAACAAGA	AGGT'GTCGGC	CTCCTCCGGC	GACCCGCAGA	AGTACTATGG	GAAGGAGCTG	AAGATCGCCA
		CCTCATCCTC				CACATCCTCA	
	CCTCTTCTGC	CCGTCCTGCC		CATCCTTACC		TCTTCCTCAC	
	TCGGCCATGA	ACCCCATTGT	CTATGCCTTC	CGCATCCAGA	AGTTCCGCGT	CACCTTCCTT	AAGATTTGGA
25	ATGACCATTT	CCGCTGCCAG C	CCTGCACCTC CO	CATTGACGA GG	ATCTCCCA GAA	AGAGAGGC CTG	ATGACTA G-3'
	(FRAG. NO:	)(SEQ. ID N	O: 2432)				
	5'-CGCATTTGT	G TTTTAATAAA	AGAATCTGGA	AGATAAATAG	TCTTGAAGAG	AGACAAAGGA	AGGAAAATTT
	AAATCCTTAG	ATTC AAGCAG	AAGAATTCCA	TGTGGAAGGT	TTGGGTTGTT	GTTGTTGTTG	TTTGGTGTGT
	TTTTTGTTTT		TGTTTTTTTT 7			TTACCGGGAG	CGACAGAGCC
30	GCACGGCCGA	GTCGAGTCCC	AGCCAGCTAC	CATCCCTCTG	GAGCTTACCG	GCCGGCCTTG	GCTTCCCCAG
	GAATCCCTGG					GGACAGAACA	
	CGGGAGCTCT				CGTGCCCCTT	GGTGCCCGTC	TGCTGATGTG
	CCCAGCCTGT	GCCCGCCATG		TCTCAGCTTT	CCAGGCCGCC	TACATCGGCA	
						AGGTGAACCA	
35	GATGCCACCT				ATGTGGCCGT	GGGTGCCCTG	GTCATCCCCC
	TCGCCATCCT	CATCAACATT		CCTACTTCCA	CACCTGCCTC	ATGGTTGCCT	
	CATCCTCACC	CAGAGCTCCA		GCTGGCAATT		GCTACCTCCG	
		ACAAGATGGT		CGGAGGGCGG	CGGTGGCCAT	AGCCGGCTGC	TGGATCCTCT
40	CCTTCGTGGT	GGGACTGACC	CCTATGTTTG	GCTGGAACAA	TCTGAGTGCG	GTGGAGCGGG	CCTGGGCAGC
40		ATGC GGGAGC	CCGTGATCAA	GTGCGAGTTC	GAGAAGGTCA	TCAGCATGGA	GTACATGGTC
	TACTTCAACT					CATCTACCTG	
	ACCTAATCCG	CAAGCAGCTC	AACAAGAAGG	TGTCGGCCTC	CTCCGGCGAC	CCGCAGAAGT	ACTATGGGAA
	GGAGCTGAAG	ATCGCCAAGT	CGCTGGCCCT	CATCCTCTTC	CTCTTTGCCC	TCAGCTGGCT	GCCTTTGCAC
15	ATCCTCAACT	GCATCACCCT	CTTCTGCCCG	TCCTGCCACA	AGCCCAGCAT	CCTTACCTAC	ATTGCCATCT
45	TCCTCACGCA	CGGC AACTCG	GCCATGAACC	CCATTGTCTA	TGCCTTCCGC	ATCCAGAAGT	TCCGCGTCAC
	CITCCITAAG	ATTT/3GAATG	ACCATTTCCG	CTGCCAGCCT	GCACCTCCCA	TTGACGAGGA	TCTCCCAGAA
	GAGAGGCCTG	ATGACTAGAC	CCCGCCTTCC	GCTCCCACCG	CCCACATCCA	GTGGGGTCTC	AGTCCAGTCC
	TCACATGCCC	GCTGTCCCAG	GGGTCTCCCT	GAGCCTGCCC	CAGCTGGGCT	GTTGGCTGGG	GGCATGGGGG
<i>-</i> 0	AGGCTCTGAA	GAGATACCCA	CAGAGTGTGG	TCCCTCCACT	AGGAGTTAAC	TACCCTACAC	CTCTGGGCCC
50	TGCAGGAGGC	CTGGGAGGGC	AAGGGTCCTA	CGGAGGGACC	AGGTGTCTAG	AGGCAACAGT	GTTCTGAGCC
	CCCACCTGCC	TGACCATCCC	ATGAGCAGTC	CAGAGCTTCA	GGGCTGGGCA	GGTCCTGGGG	AGGCTGAGAC
	TGCAGAGGAG	CCACCTGGGC	TGGGAGAAGG	TGCTTGGGCT	TCTGCGGTGA	${\tt GGCAGGGGAG}$	TCTGCTTGTC
	TTAGATGTTG	GTGGTGCAGC	CCCAGGACCA	AGCTTAAGGA	GAGGAGAGCA	TCTGCTCTGA	GACGGATGGA
<i></i>		TTGAGGATGC A		TGTAGGAG AGA	CTGGCCA GA -3	,	
55		_)(SEQ. ID No					
	o - ATGAGTGTC	A GAAGTGTGA.	A GGGTGCCTGT	TCTGAATCCC	AGAGCCTCCT	CTCCCTCTGT	GAGGCTGGCA
	GGGGGGGAAG	GGTTTAACCT	CACTGGAAGG	AATCCCTGGA	GCTAGCGGCT	GCTGAAGGCG	TCGAGGTGTG
						TGACCTTGGG	
	MITE LTE   14 0	I LEGEL ALECT YESTS	ATTENTO	120 1120 1120 120 120 120 120 120 120 12	A STREET STREET A A A A	CCCCACCCCA	COCCUTACOCC



CCATCTCAGC TTTC'CAGGCC GCCTACATCG GCATCGAGGT GCTCATCGCC CTGGTCTCTG TGCCCGGGAA CGTGCTGGTG ATCTGGGCGG TGAAGGTGAA CCAGGCGCTG CGGGATGCCA CCTTCTGCTT CATCGTGTCG CTGGCGGTGG CTGATGTGGC CGTGGGTGCC CTGGTCATCC CCCTCGCCAT CCTCATCAAC ATTGGGCCAC AGACCTACTT CCACACCTGC CTCATGGTTG CCTGTCCGGT CCTCATCCTC ACCCAGAGCT CCATCCTGGC CCTGCTGGCA ATTGCTGTGG ACCGCTACCT CCGGGTCAAG ATCCCTCTCC GGTACAAGAT GGTGGTGACC CCCCGGAGGG CGGCGGTGGC CATAGCCGGC TGCTGGATCC TCTCCTTCGT GGTGGGACTG ACCCCTATGT TTGGCTGGAA CAATCTGAGT GCGGTGGAGC GGGCCTGGGC AGCCAACGGC AGCATGGGGG AGCCCGTGAT CAAGTGCGAG TTCGAGAAGG TCATCAGCAT GGAGTACATG GTCTACTTCA ACTTCTTTGT GTGGGTGCTG CCCCCGCTTC TCCTCATGGT CCTCATCTAC CTGGAGGTCT TCTACCTAAT CCGCAAGCAG CTCAACAAGA AGGTGTCGGC CTCCTCCGGC GACCCGCAGA AGTACTATGG GAAGGAGCTG AAGATCGCCA AGTCGCTGGC 10 CCTCATCCTC TTCCTCTTG CCCTCAGCTG GCTGCCTTTG CACATCCTCA ACTGCATCAC CCTCTTCTGC CCGTCCTGCC ACAAGCCCAG CATCCTTACC TACATTGCCA TCTTCCTCAC GCACGGCAAC TCGGCCATGA ACCCCATTGT CTATGCCTTC CGCATCCAGA AGTTCCGCGT CACCTTCCTT AAGATTTGGA ATGACCATTT CCGCTGCCAG CCTCCACCTC CCATTGACGA GGATCTCCCA GAAGAGAGGC CTGATGACTA GACCCCGCCT 15 TCCGCTCCCA CCACICCCACA TCCAGTGGGG TCTCAGTCCA GTCCTCACAT GCCCGCTGTC CCAGGGGTCT CCCTGAGCCT GCCCCAGCTG GGCTGTTGGC TGGGGGCATG GGGGAGGCTC TGAAGAGATA CCCACAGAGT GTGGTCCCTC CACTAGGAGT TAACTACCCT ACACCTCTGG GCCCTGCAGG AGGCCTGGGA GGGCAAGGGT CCTACGGAGG GACCAGGTGT CTAGAGGCAA CAGTGTTCTG AGCCCCCACC TGCCTGACCA TCCCATGAGC AGTCCAGCGC TTCAGGGCTG GGCAGGTCCT GGGGAGGCTG AGACTGCAGA GGAGCCACCT GGGCTGGGAG AAGGTGCTTG GGCTTCTGCG GTGAGGCAGG GGAGTCTGCT TGTCTTAGAT GTTGGTGGTG CAGCCCCAGG ACCAAGCTTA AGGAGAGAG AGCATCTGCT CTGAGACGGA TGGAAGGAGA GAGGTTGAGG ATGCACTGGC CTGTTCTGTA GGAGAGACTG GCCAGAGGCA GCTAAGGGGC AGGAATCAAG GAGCCTCCGT TCCCACCTCT GAGGACTCTG GACCCCAGGC CATACCAGGT GCTAGGGTGC CTGCTCTCCT TGCCCTGGGC CAGCCCAGGA TTGTACGTGG GAGAGGCAGA AAGGGTAGGT TCAGTAATCA TTTCTGATGA TTTGCTGGAG TGCTGGCTCC ACGCCCTGGG GAGTGAGCTT GGTGCGGTAG GTGCTGGCCT CAAACAGCCA CGAGGTGGTA GCTCTGAGCC CTCCTTCTTG CCCTGAGCTT TCCGGGGAGG AGCCTGGAGT GTAATTACCT GTCATCTGGG CCACCAGCTC CACTGGCCCC CGTIGCCGGG CCTGGACTGT CCTAGGTGAC CCCATCTCTG CTGCTTCTGG GCCTGATGGA GAGGAGAACA CTAGACATGC CAACTCGGGA GCATTCTGCC TGCCTGGGAA CGGGGTGGAC GAGGGAGTGT CTGTAAGGAC TCACTGTTGA CTGTAGGCGC CCCTGGGGTG GGTTTAGCAG GCTGCAGCAG GCAGAGGAGG AGTACCCCCC TGACAGCATG TGGGGGAAGG CCTTGCTGTC ATGTGAATCC CTCAATACCC CTAGTATCTG GCTGGGTTTT CAGGGGCTTT GGAAGCTCTG TTGCAGGTGT CCGGGGGTCT AGGACTTTAG GGATCTGGGA TCTGGGGAAG GACC'AACCCA TGCCCTGCCA AGCCTGGAGC CCCTGTGTTG GGGGGCAAGG TGGGGGAGCC TGGAGCCCCT GTGT3GGAGG GCGAGGCGGG GGAGCCTGGA GCCCCTGTGT GGGAGGGCGA GGCGGGGGAT CCTGGAGCCC CTGTGTCGGG GGGCGAGGGA GGGGAGGTGG CCGTCGGTTG ACCTTCTGAA CATGAGTGTC AACTCCAGGA CTTCCTTCCA AGCCCTTCCC TCTGTTGGAA ATTGGGTGTG CCCTGGCTCC CAAGGGAGGC CCATGTGACT AATAAAAAC TGTGAACCCT -3' (FRAG. NO:\_\_) (SEQ. ID NO: 2421) 5'-ATGCCGCCCT CCATCTCAGC TTTCCAGGCC GCCTACATCG GCATCGAGGT GCTCATCGCC CTGGTCTCTG CCCCTATGT TTGGCIGGAA CAATCTGAGT GCGGTGGAGC GGGCCTGGGC AGCCAACGGC AGCATGGGGG AGCCCGTGAT CAACTGCGAG TTCGAGAAGG TCATCAGCAT GGAGTACATG GTCTACTTCA ACTTCTTTGT GTGGGTGCTG CCCCCGCTTC TCCTCATGGT CCTCATCTAC CTGGAGGTCT TCTACCTAAT CCGCAAGCAG CTCAACAAGA AGG1GTCGGC CTCCTCCGGC GACCCGCAGA AGTACTATGG GAAGGAGCTG AAGATCGCCA AGTCGCTGGC CCTCATCCTC TTCCTCTTG CCCTCAGCTG GCTGCCTTTG CACATCCTCA ACTGCATCAC CCTCTTCTGC CCGTCCTGCC ACAAGCCCAG CATCCTTACC TACATTGCCA TCTTCCTCAC GCACGGCAAC TCGGCCATGA ACCCCATTGT CTATGCCTTC CGCATCCAGA AGTTCCGCGT CACCTTCCTT AAGATTTGGA ATGACCATTT CCGCTGCCAG CCTGCACCTC CCATTGACGA GGATCTCCCA GAAGAGAGGC CTGATGACTA G (FRAG NO: ) (SEQ. ID NO: 2420) 5'-GAT GGA GGG CGG CAT GGC GGG-3' (FRAG. NO: 1657) (SEQ ID NO:2412) 5'-G CGG GTC GCC GC-3' (FRAG. NO: 1658) (SEQ ID NO:2413) 5'-GGC GGG CBC BGG C-3' (FRAG. NO: 1659) (SEQ ID NO:2414) 5'-GGC GGG CBC-3' (FRAG. NO: 1660) (SEQ ID NO:2415)

5'-GC GGC CTG G-3' (FRAG. NO: 1661) (SEQ ID NO:2416)

5'-GGB GGG CGG C-3' (FRAG. NO: 1662) (SEQ ID NO:2417)

5'-GBT GGB GGG-3' (FRAG. NO: 1663) (SEQ ID NO:2418)

5'-GG CTG GGC-3' (FRAG. NO: 1664) (SEQ ID NO:2419)

5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG.1) (SEQ. ID NO: 11) 5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3'(FRAG 2) (SEQ. .ID NO:12)



5'-GGC CTG GAA AGC' TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3'(FRAG 3)(SEQ.ID NO:13) 5'-GC CTG GAA AGC 'IGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 4)(SEQ. ID NO:14) 5'-C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 5) (SEQ. ID NO: 15) 5'-CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 6) (SEQ. ID NO: 16) 5'-TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 7) (SEQ. ID NO: 17) 5'-G GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 8) (SEQ. ID NO: 18) 5'-GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 9) (SEQ. ID NO: 19) 5'-AA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 10) (SEQ. ID NO: 20) 5'-A AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 11) (SEQ. ID NO: 21) 5'-AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 12) (SEQ. ID NO: 22) 5'-GC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 13) (SEQ. ID NO: 23) 5'-C TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 14) (SEQ. ID NO: 24) 5'-TGA GAT GGA GGC CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 15) (SEQ. ID NO: 25) 5'-GA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 16) (SEQ. ID NO: 26) 5'-A GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 17) (SEQ. ID NO: 27) 5'-GAT GGA GGG CGC CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 18) (SEQ. ID NO: 28) 5'-AT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 19) (SEQ. ID NO: 29) 5'-T GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 20) (SEQ. ID NO: 30) 5'-GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 21) (SEQ. ID NO: 31) 5'-GA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 22) (SEO. ID NO: 32) 5'-A GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 23) (SEO. ID NO: 33) 5'-GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 24) (SEQ. ID NO: 34) 5'-GG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 25) (SEQ. ID NO: 35) 5'-G CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 26) (SEQ. ID NO: 36) 5'-CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 27) (SEQ. ID NO: 37) 5'-GG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 28) (SEQ. ID NO: 38) 5'-G CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 29) (SEQ. ID NO: 39) 5'-CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 30) (SEQ. ID NO: 40) 5'-AT GGC GGG CAC AGG CTG GGC-3' (FRAG 31) (SEQ. ID NO: 41) 5'-T GGC GGG CAC AGG CTG GGC-3' (FRAG 32) (SEQ. ID NO: 42) 5'-GGC GGG CAC AGC CTG GGC-3' (FRAG 33) (SEQ. ID NO: 43) 5'-GC GGG CAC AGG CTG GGC-3' (FRAG 34) (SEQ. ID NO: 44) 5'-C GGG CAC AGG CT'G GGC-3' (FRAG 35) (SEQ. ID NO: 45) 5'-GGG CAC AGG CTG GGC-3' (FRAG 36) (SEQ. ID NO: 46) 5'-GG CAC AGG CTG (GC-3' (FRAG 37) (SEO, ID NO: 47) 5'-G CAC AGG CTG GGC-3' (FRAG 38) (SEQ. ID NO: 48) 5'-CAC AGG CTG GGC-3' (FRAG 39) (SEQ. ID NO: 49) 5'-AC AGG CTG GGC-3' (FRAG 40) (SEQ. ID NO: 50) 5'-C AGG CTG GGC-3' (FRAG 41) (SEQ. ID NO: 51) 5'-AGG CTG GGC-3' (FRAG 42) (SEQ. ID NO: 52) 5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3'(FRAG 43)(SEQ.ID NO:53) 5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 44)(SEO.ID NO:54) 5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 45)(SEQ.ID NO:55) 5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 46)(SEQ.ID NO:56) 5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 47)(SEQ.ID NO:57) 5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 48)(SEQ. ID NO:58) 5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 49) (SEQ. ID NO: 59) 5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 50) (SEQ. ID NO: 60) 5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 51) (SEQ. ID NO: 61) 5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 52) (SEQ. ID NO: 62) 5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 53) (SEQ. ID NO: 63) 5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG C-3' (FRAG 54) (SEQ. ID NO: 64) 5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG -3' (FRAG 55) (SEQ. ID NO: 65) 5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GG-3' (FRAG 56) (SEQ. ID NO: 66) 5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC G-3'(FRAG 57) (SEQ. ID NO: 67) 5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC -3' (FRAG 58) (SEQ. ID NO: 68) 5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GG -3' (FRAG 59) (SEQ. ID NO: 69) 5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT G -3' (FRAG 60) (SEQ. ID NO: 70) 5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT -3' (FRAG 61) (SEQ. ID NO: 71) 5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CA-3' (FRAG 62) (SEQ. ID NO: 72)

5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG C-3' (FRAG 63) (SEQ. ID NO: 73) 5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG -3' (FRAG 64) (SEQ. ID NO: 74)



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5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CG -3' (FRAG 65) (SEQ. ID NO: 75)
5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG C -3' (FRAG 66) (SEO. ID NO: 76)
5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG -3' (FRAG 67) (SEQ. ID NO: 77)
5'-GGC GGC CTG GAA AGC TGA GAT GGA GG -3' (FRAG 68) (SEQ. ID NO: 78)
5^{\circ}\text{-}GGC GGC CTG GAA AGC TGA GAT GGA G \text{-}3^{\circ} (FRAG 69) (SEQ. ID NO: 79)
5'-GGC GGC CTG GAA AGC TGA GAT GGA -3' (FRAG 70) (SEQ. ID NO: 80)
5'-GGC GGC CTG GAA AGC TGA GAT GG -3' (FRAG 71) (SEQ. ID NO: 81)
5'-GGC GGC CTG GAA AGC TGA GAT G -3' (FRAG 72) (SEQ. ID NO: 82)
5'-GGC GGC CTG GAA AGC TGA GAT -3' (FRAG 73) (SEQ. ID NO: 83)
5'-GGC GGC CTG GAA AGC TGA GA-3' (FRAG 74) (SEQ. ID NO: 84)
5'-GGC GGC CTG GAA AGC TGA G-3' (FRAG 75) (SEQ. ID NO: 85)
5'-GGC GGC CTG GAA AGC TGA-3' (FRAG 76) (SEQ. ID NO: 86)
5'-GGC GGC CTG GAA AGC TG-3' (FRAG 77) (SEO. ID NO: 87)
5'-GGC GGC CTG GAA AGC T-3' (FRAG 78) (SEQ. ID NO: 88)
5'-GGC GGC CTG GAA AGC-3' (FRAG 79) (SEQ. ID NO: 89)
5'-GGC GGC CTG GAA AG-3' (FRAG 80) (SEQ. ID NO: 90)
5'-GGC GGC CTG GAA A-3' (FRAG 81) (SEQ. ID NO: 91)
5'-GGC GGC CTG GAA-3' (FRAG 82) (SEQ. ID NO: 92)
5'-GGC GGC CTG GA-(' (FRAG 83) (SEQ. ID NO: 93)
5'-GGC GGC CTG G-3' (FRAG 84) (SEQ. ID NO: 94)
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 85) (SEQ. ID NO:
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 86) (SEO. ID NO: 96)
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 87) (SEO. ID NO: 97)
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 88) (SEO. ID NO: 98)
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 89) (SEO. ID NO: 99)
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 90) (SEQ. ID NO: 100)
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 91) (SEQ. ID NO: 101)
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 92) (SEO. ID NO: 102)
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 93) (SEQ. ID NO: 103)
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 94) (SEQ. ID NO: 104)
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 95) (SEO. ID NO: 105)
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG C-3' (FRAG 96) (SEO. ID NO: 106)
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG -3' (FRAG 97) (SEO. ID NO: 107)
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GG-3' (FRAG 98) (SEQ. ID NO: 108)
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC G-3' (FRAG 99) (SEQ. ID NO: 109)
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC -3' (FRAG 100) (SEQ. ID NO: 110)
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GG -3' (FRAG 101) (SEQ. ID NO: 111)
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT G -3' (FRAG 102) (SEQ. ID NO: 112)
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT -3' (FRAG 103) (SEQ. ID NO: 113)
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CA-3' (FRAG 104) (SEQ. ID NO: 114)
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG C-3' (FRAG 105) (SEO. ID NO: 115)
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG -3' (FRAG 106) (SEQ. ID NO: 116)
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CG -3' (FRAG 107) (SEQ. ID NO: 117)
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG C -3' (FRAG 108) (SEQ. ID NO: 118)
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG -3' (FRAG 109) (SEQ. ID NO: 119)
5'-GC GGC CTG GAA AGC TGA GAT GGA GG -3' (FRAG 110) (SEQ. ID NO: 120)
5'-GC GGC CTG GAA AGC TGA GAT GGA G -3' (FRAG 111) (SEQ. ID NO: 121)
5'-GC GGC CTG GAA AGC TGA GAT GGA -3' (FRAG 112) (SEQ. ID NO: 122)
5'-GC GGC CTG GAA AGC TGA GAT GG -3' (FRAG 113) (SEQ. ID NO: 123)
5'-GC GGC CTG GAA AGC TGA GAT G -3' (FRAG 114) (SEO, ID NO: 124)
5'-GC GGC CTG GAA AGC TGA GAT -3' (FRAG 115) (SEO. ID NO: 125)
5'-GC GGC CTG GAA AGC TGA GA-3' (FRAG 116) (SEO. ID NO: 126)
5'-GC GGC CTG GAA AGC TGA G-3' (FRAG 117) (SEQ. ID NO: 127)
5'-GC GGC CTG GAA AGC TGA-3' (FRAG 118) (SEQ. ID NO: 128)
5'-GC GGC CTG GAA AGC TG-3' (FRAG 119) (SEQ. ID NO: 129)
5'-GC GGC CTG GAA A.GC T-3' (FRAG 120) (SEQ. ID NO: 130)
5'-GC GGC CTG GAA A.GC-3' (FRAG 121) (SEQ. ID NO: 131)
5'-GC GGC CTG GAA A.G-3' (FRAG 122) (SEQ. ID NO: 132)
5'-GC GGC CTG GAA A-3' (FRAG 123) (SEQ. ID NO: 133)
5'-GC GGC CTG GAA-3' (FRAG 124) (SEQ. ID NO: 134)
5'-GC GGC CTG GA-3' (FRAG 125) (SEQ. ID NO: 135)
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5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 126) (SEO. ID NO:
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 127) (SEO. ID NO:
137)
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 128) (SEQ. ID NO: 138)
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 129) (SEQ. ID NO: 139)
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 130) (SEO. ID NO: 140)
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 131) (SEQ. ID NO: 141)
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 132) (SEQ. ID NO: 142)
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 133) (SEQ. ID NO: 143)
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 134) (SEO. ID NO: 144)
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 135) (SEQ. ID NO: 145)
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 136) (SEO. ID NO: 146)
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG C-3' (FRAG 137) (SEQ. ID NO: 147)
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG -3' (FRAG 138) (SEO. ID NO: 148)
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GG-3' (FRAG 139) (SEO. ID NO: 149)
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC G-3' (FRAG 140) (SEQ. ID NO: 150)
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC -3' (FRAG 141) (SEQ. ID NO: 151)
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GG -3' (FRAG 142) (SEQ. ID NO: 152)
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT G -3' (FRA 143) (SEQ. ID NO: 153)
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT -3' (FRAG 144) (SEQ. ID NO: 154)
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CA-3' (FRAG 145) (SEQ. ID NO: 155)
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG C-3' (FRAG 146) (SEQ. ID NO: 156)
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG -3' (FRAG 147) (SEQ. ID NO: 157)
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CG -3' (FRAG 148) (SEQ. ID NO: 158)
5'-C GGC CTG GAA AGC TGA GAT GGA GGG C -3' (FRAG 148) (SEO. ID NO: 159)
5'-C GGC CTG GAA AGC TGA GAT GGA GGG -3' (FRAG 150) (SEQ. ID NO: 160)
5'-C GGC CTG GAA AGC TGA GAT GGA GG -3' (FRAG 151) (SEQ. ID NO: 161)
5'-C GGC CTG GAA AGC TGA GAT GGA G -3' (FRAG 152) (SEQ. ID NO: 162)
5'-C GGC CTG GAA AGC TGA GAT GGA -3' (FRAG 153) (SEQ. ID NO: 163)
5'-C GGC CTG GAA AGC TGA GAT GG -3' (FRAG 154) (SEQ. ID NO: 164)
5'-C GGC CTG GAA AGC TGA GAT G -3' (FRAG 155) (SEO. ID NO: 165)
5'-C GGC CTG GAA AGC TGA GAT -3' (FRAG 156) (SEO. ID NO: 166)
5'-C GGC CTG GAA AGC TGA GA-3' (FRAG 157) (SEO. ID NO: 167)
5'-C GGC CTG GAA AGC TGA G-3' (FRAG 158) (SEQ. ID NO: 168)
5'-C GGC CTG GAA AGC TGA-3' (FRAG 159) (SEQ. ID NO: 169)
5'-C GGC CTG GAA AGC TG-3' (FRAG 160) (SEQ. ID NO: 170)
5'-C GGC CTG GAA AGC T-3' (FRAG 161) (SEQ. ID NO: 171)
5'-C GGC CTG GAA AGC-3' (FRAG 162) (SEQ. ID NO: 172)
5'-C GGC CTG GAA AG-3' (FRAG 163) (SEO. ID NO: 173)
5'-C GGC CTG GAA A-3' (FRAG 164) (SEQ. ID NO: 174)
5'-C GGC CTG GAA-3' (FRAG 165) (SEQ. ID NO: 175)
5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 166) (SEQ. ID NO:
176)
5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 167) (SEQ. ID NO: 177)
5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 168) (SEQ. ID NO: 178)
5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 169) (SEQ. ID NO: 179)
5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 170) (SEQ. ID NO: 180)
5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 171) (SEQ. ID NO: 181)
5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 172) (SEQ. ID NO: 182)
5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 173) (SEO. ID NO: 183)
5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 174) (SEQ. ID NO: 184)
5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 175) (SEQ. ID NO: 185)
5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 176) (SEQ. ID NO: 186)
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5'- GGC CTG GAA AGC: TGA GAT GGA GGG CGG CAT GGC GGG C-3' (FRAG 177) (SEQ. ID NO: 187)
5'- GGC CTG GAA AGC: TGA GAT GGA GGG CGG CAT GGC GGG -3' (FRAG 178) (SEQ. ID NO: 188)
5'- GGC CTG GAA AGC: TGA GAT GGA GGG CGG CAT GGC GG-3' (FRAG 179) (SEQ. ID NO: 189)
5'- GGC CTG GAA AGC: TGA GAT GGA GGG CGG CAT GGC G-3' (FRAG 180) (SEQ. ID NO: 190)
5'- GGC CTG GAA AGC: TGA GAT GGA GGG CGG CAT GGC -3' (FRAG 181) (SEQ. ID NO: 191)
5'- GGC CTG GAA AGC: TGA GAT GGA GGG CGG CAT GG -3' (FRAG 182) (SEQ. ID NO: 192)
5'- GGC CTG GAA AGC: TGA GAT GGA GGG CGG CAT G -3' (FRAG 183) (SEQ. ID NO: 193)

5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT -3' (FRAG 184) (SEQ. ID NO: 194)



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5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CA-3' (FRAG 185) (SEQ. ID NO: 195)
 5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG C-3' (FRAG 186) (SEQ. ID NO: 196)
 5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG -3' (FRAG 187) (SEQ. ID NO: 197)
 5'- GGC CTG GAA AGC TGA GAT GGA GGG CG -3' (FRAG 188) (SEQ. ID NO: 198)
 5'- GGC CTG GAA AGC TGA GAT GGA GGG C -3' (FRAG 189) (SEQ. ID NO: 199)
 5'- GGC CTG GAA AGC TGA GAT GGA GGG -3' (FRAG 190) (SEQ. ID NO: 200)
 5'- GGC CTG GAA AGC TGA GAT GGA GG -3' (FRAG 191) (SEQ. ID NO: 201)
 5'- GGC CTG GAA AGC TGA GAT GGA G -3' (FRAG 192) (SEQ. ID NO: 202)
 5'- GGC CTG GAA AGC TGA GAT GGA -3' (FRAG 193) (SEQ. ID NO: 203)
5'- GGC CTG GAA AGC TGA GAT GG -3' (FRAG 194) (SEQ. ID NO: 204)
 5'- GGC CTG GAA AGC TGA GAT G -3' (FRAG 195) (SEQ. ID NO: 205)
 5'- GGC CTG GAA AGC TGA GAT -3' (FRAG 196) (SEQ. ID NO: 206)
 5'- GGC CTG GAA AGC TGA GA-3' (FRAG 197) (SEQ. ID NO: 207)
 5'- GGC CTG GAA AGC TGA G-3' (FRAG 198) (SEQ. ID NO: 208)
 5'- GGC CTG GAA AGC TGA-3' (FRAG 199) (SEQ. ID NO: 209)
 5'- GGC CTG GAA AGC TG-3' (FRAG 200 (SEQ. ID NO: 210)
 5'- GGC CTG GAA AGC T-3' (FRAG 201) (SEQ. ID NO: 211)
 5'- GGC CTG GAA AGC-3' (FRAG 202) (SEQ. ID NO: 212)
 5'- GGC CTG GAA AG-3' (FRAG 203) (SEQ. ID NO: 213)
 5'- GGC CTG GAA A-3' (FRAG 204) (SEQ. ID NO: 214)
 5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 205) (SEQ. ID NO:
 5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 206) (SEQ. ID NO: 216)
 5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 207) (SEQ. ID NO: 217)
5'- GC CTG GAA AGC 'TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 208) (SEQ. ID NO: 218)
 5'- GC CTG GAA AGC 'TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 209) (SEQ. ID NO: 219)
 5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 210) (SEQ. ID NO: 220)
 5'- GC CTG GAA AGC 'IGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 211) (SEQ. ID NO: 221)
 5'- GC CTG GAA AGC 'I'GA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 212) (SEQ. ID NO: 222)
5'- GC CTG GAA AGC 'FGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 213) (SEO. ID NO: 223)
 5'- GC CTG GAA AGC 'IGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 214) (SEO. ID NO: 224)
 5'- GC CTG GAA AGC 'FGA GAT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 215) (SEQ. ID NO: 225)
 5'- GC CTG GAA AGC 'I'GA GAT GGA GGG CGG CAT GGC GGG C-3' (FRAG 216) (SEQ. ID NO: 226)
 5'- GC CTG GAA AGC 'IGA GAT GGA GGG CGG CAT GGC GGG -3' (FRAG 217) (SEQ. ID NO: 227)
5'- GC CTG GAA AGC 'TGA GAT GGA GGG CGG CAT GGC GG-3' (FRAG 218) (SEQ. ID NO: 228)
 5'- GC CTG GAA AGC 'TGA GAT GGA GGG CGG CAT GGC G-3' (FRAG 219) (SEQ. ID NO: 229)
 5'- GC CTG GAA AGC 'TGA GAT GGA GGG CGG CAT GGC -3' (FRAG 220) (SEQ. ID NO: 230)
 5'- GC CTG GAA AGC 'IGA GAT GGA GGG CGG CAT GG -3' (FRAG 221) (SEQ. ID NO: 231)
 5'- GC CTG GAA AGC 'IGA GAT GGA GGG CGG CAT G -3' (FRAG 222) (SEQ. ID NO: 232)
5'- GC CTG GAA AGC 'IGA GAT GGA GGG CGG CAT -3' (FRAG 223) (SEQ. ID NO: 233)
 5'- GC CTG GAA AGC 'IGA GAT GGA GGG CGG CA-3' (FRAG 224) (SEQ. ID NO: 234)
 5'- GC CTG GAA AGC 'IGA GAT GGA GGG CGG C-3' (FRAG 225) (SEQ. ID NO: 235)
 5'- GC CTG GAA AGC 'IGA GAT GGA GGG CGG -3' (FRAG 226) (SEQ. ID NO: 236)
 5'- GC CTG GAA AGC 'IGA GAT GGA GGG CG -3' (FRAG 227) (SEQ. ID NO: 237)
5'- GC CTG GAA AGC 'IGA GAT GGA GGG C -3' (FRAG 228) (SEQ. ID NO: 238)
 5'- GC CTG GAA AGC 'IGA GAT GGA GGG -3' (FRAG 229) (SEQ. ID NO: 239)
 5'- GC CTG GAA AGC TGA GAT GGA GG -3' (FRAG 230) (SEQ. ID NO: 240)
 5'- GC CTG GAA AGC TGA GAT GGA G -3' (FRAG 231) (SEQ. ID NO: 241)
 5'- GC CTG GAA AGC TGA GAT GGA -3' (FRAG 232) (SEO. ID NO: 242)
5'- GC CTG GAA AGC '[GA GAT GG -3' (FRAG 233) (SEO. ID NO: 243)
 5'- GC CTG GAA AGC 'TGA GAT G -3' (FRAG 234) (SEQ. ID NO: 244)
 5'- GC CTG GAA AGC 'IGA GAT -3' (FRAG 235) (SEQ. ID NO: 245)
 5'- GC CTG GAA AGC 'CGA GA-3' (FRAG 236) (SEQ. ID NO: 246)
5'- GC CTG GAA AGC '`GA G-3' (FRAG 237) (SEQ. ID NO: 247)
5'- GC CTG GAA AGC '`GA-3' (FRAG 238) (SEQ. ID NO: 248)
 5'- GC CTG GAA AGC 'G-3' (FRAG 239) (SEQ. ID NO: 249)
 5'- GC CTG GAA AGC '`-3' (FRAG 240) (SEQ. ID NO: 250)
 5'- GC CTG GAA AGC-3' (FRAG 241) (SEQ. ID NO: 251)
 5'- GC CTG GAA AG-3' (FRAG 242) (SEQ. ID NO: 252)
5'- C CTG GAA AGC TGA GAT GG A GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 243) (SEQ. ID NO: 253)
5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 244) (SEQ. ID NO: 254)
 5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 245) (SEO. ID NO: 255)
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5'- C CTG GAA AGC T3A GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 246) (SEO. ID NO: 256)
     5'- C CTG GAA AGC T'3A GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 247) (SEO. ID NO: 257)
     5'- C CTG GAA AGC T3A GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 248) (SEQ. ID NO: 258)
     5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 249) (SEQ. ID NO: 259)
     5'- C CTG GAA AGC T-3A GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 250) (SEQ. ID NO: 260)
     5'- C CTG GAA AGC T'3A GAT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 251) (SEQ. ID NO: 261)
     5'- C CTG GAA AGC T3A GAT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 252) (SEQ. ID NO: 262)
     5'- C CTG GAA AGC T3A GAT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 253) (SEQ. ID NO: 263)
     5'- C CTG GAA AGC T'GA GAT GGA GGG CGG CAT GGC GGG C-3' (FRAG 254) (SEQ. ID NO: 264)
     5'- C CTG GAA AGC T3A GAT GGA GGG CGG CAT GGC GGG -3' (FRAG 255) (SEQ. ID NO: 265)
     5'- C CTG GAA AGC T'3A GAT GGA GGG CGG CAT GGC GG-3' (FRAG 256) (SEQ. ID NO: 266)
     5'- C CTG GAA AGC T'3A GAT GGA GGG CGG CAT GGC G-3' (FRAG 257) (SEQ. ID NO: 267)
     5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC -3' (FRAG 258) (SEQ. ID NO: 268)
     5'- C CTG GAA AGC T3A GAT GGA GGG CGG CAT GG -3' (FRAG 259) (SEQ. ID NO: 269)
     5'- C CTG GAA AGC T'3A GAT GGA GGG CGG CAT G -3' (FRAG 260) (SEQ. ID NO: 270)
     5'- C CTG GAA AGC T'3A GAT GGA GGG CGG CAT -3' (FRAG 261) (SEQ. ID NO: 271)
     5'- C CTG GAA AGC T'3A GAT GGA GGG CGG CA-3' (FRAG 262) (SEQ. ID NO: 272)
     5'- C CTG GAA AGC T'GA GAT GGA GGG CGG C-3' (FRAG 263) (SEQ. ID NO: 273)
     5'- C CTG GAA AGC TGA GAT GGA GGG CGG -3' (FRAG 264) (SEQ. ID NO: 274)
     5'- C CTG GAA AGC T'3A GAT GGA GGG CG -3' (FRAG 265) (SEQ. ID NO: 275)
     5'- C CTG GAA AGC T'GA GAT GGA GGG C -3' (FRAG 266) (SEQ. ID NO: 276)
     5'- C CTG GAA AGC T'3A GAT GGA GGG -3' (FRAG 267) (SEQ. ID NO: 277)
     5'- C CTG GAA AGC T'3A GAT GGA GG -3' (FRAG 268) (SEQ. ID NO: 278)
     5'- C CTG GAA AGC T'3A GAT GGA G -3' (FRAG 269) (SEQ. ID NO: 279)
     5'- C CTG GAA AGC T'GA GAT GGA -3' (FRAG 270) (SEQ. ID NO: 280)
     5'- C CTG GAA AGC TGA GAT GG -3' (FRAG 271) (SEQ. ID NO: 281)
     5'- C CTG GAA AGC TGA GAT G -3' (FRAG 272) (SEQ. ID NO: 282)
     5'- C CTG GAA AGC T'3A GAT -3' (FRAG 273) (SEQ. ID NO: 283)
     5'- C CTG GAA AGC TGA GA-3' (FRAG 274) (SEQ. ID NO: 284)
     5'- C CTG GAA AGC T'GA G-3' (FRAG 275) (SEO. ID NO: 285)
     5'- C CTG GAA AGC T'GA-3' (FRAG 276) (SEO. ID NO: 286)
     5'- C CTG GAA AGC T 3-3' (FRAG 277) (SEQ. ID NO: 287)
     5'- C CTG GAA AGC T 3' (FRAG 278) (SEQ. ID NO: 288)
     5'- C CTG GAA AGC-3' (FRAG 279) (SEQ. ID NO: 289)
     5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 280) (SEQ. ID NO: 290)
     5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 281) (SEQ. ID NO: 291)
     5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 282) (SEQ. ID NO: 292)
     5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 283) (SEQ. ID NO: 293)
     5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 284) (SEQ. ID NO: 294)
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     5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 285) (SEQ. ID NO: 295)
     5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 286) (SEQ. ID NO: 296)
     5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 287) (SEQ. ID NO: 297)
     5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 288) (SEQ. ID NO: 298)
     5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 289) (SEQ. ID NO: 299)
     5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 290) (SEQ. ID NO: 300)
     5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG C-3' (FRAG 291) (SEQ. ID NO: 301)
     5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG -3' (FRAG 292) (SEQ. ID NO: 302)
     5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GG-3' (FRAG 293) (SEQ. ID NO: 303)
     5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC G-3' (FRAG 294) (SEQ. ID NO: 304)
     5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC -3' (FRAG 295) (SEO. ID NO: 305)
     5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GG -3' (FRAG 296) (SEQ. ID NO: 306)
     5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT G -3' (FRAG 297) (SEQ. ID NO: 307)
     5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT -3' (FRAG 298) (SEQ. ID NO: 308)
     5'- CTG GAA AGC TGA GAT GGA GGG CGG CA-3' (FRAG 299) (SEQ. ID NO: 309)
     5'- CTG GAA AGC TGA GAT GGA GGG CGG C-3' (FRAG 300) (SEQ. ID NO: 310)
     5'- CTG GAA AGC TGA GAT GGA GGG CGG -3' (FRAG 301) (SEQ. ID NO: 311)
     5'- CTG GAA AGC TGA GAT GGA GGG CG -3' (FRAG 302) (SEQ. ID NO: 312)
     5'- CTG GAA AGC TGA GAT GGA GGG C -3' (FRAG 303) (SEQ. ID NO: 313)
     5'- CTG GAA AGC TGA GAT GGA GGG -3' (FRAG 304) (SEQ. ID NO: 314)
     5'- CTG GAA AGC TGA GAT GGA GG -3' (FRAG 305) (SEQ. ID NO: 315)
     5'- CTG GAA AGC TGA GAT GGA G -3' (FRAG 306) (SEQ. ID NO: 316)
     5'- CTG GAA AGC TGA GAT GGA -3' (FRAG 307) (SEQ. ID NO: 317)
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5'- CTG GAA AGC TG4 GAT GG -3' (FRAG 308) (SEQ. ID NO: 318)
     5'- CTG GAA AGC TG A GAT G -3' (FRAG 309) (SEQ. ID NO: 319)
     5'- CTG GAA AGC TGA GAT -3' (FRAG 310) (SEQ. ID NO: 320)
     5'- CTG GAA AGC TGA GA-3' (FRAG 311) (SEQ. ID NO: 321)
     5'- CTG GAA AGC TG 4 G-3' (FRAG 312) (SEQ. ID NO: 322)
     5'- CTG GAA AGC TG 4-3' (FRAG 313) (SEQ. ID NO: 323)
     5'- CTG GAA AGC TG 3' (FRAG 314) (SEQ. ID NO: 324)
     5'- CTG GAA AGC T-3' (FRAG 315) (SEQ. ID NO: 325)
     5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 316) (SEQ. ID NO: 326)
     5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 317) (SEQ. ID NO: 327)
     5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 318) (SEO. ID NO: 328)
     5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 319) (SEO. ID NO: 329)
     5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 320) (SEO. ID NO: 330)
     5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 321) (SEQ. ID NO: 331)
     5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 322) (SEQ. ID NO: 332)
     5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 323) (SEQ. ID NO: 333)
     5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 324) (SEQ. ID NO: 334)
     5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 325) (SEQ. ID NO: 335)
     5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 326) (SEQ. ID NO: 336)
     5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG C-3' (FRAG 327) (SEQ. ID NO: 337)
     5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG -3' (FRAG 328) (SEQ. ID NO: 338)
     5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GG-3' (FRAG 329) (SEQ. ID NO: 339)
     5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC G-3' (FRAG 330) (SEQ. ID NO: 340)
     5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC -3' (FRAG 331) (SEQ. ID NO: 341)
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     5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GG -3' (FRAG 332) (SEQ. ID NO: 342)
     5'- TG GAA AGC TGA GAT GGA GGG CGG CAT G -3' (FRAG 333) (SEQ. ID NO: 343)
     5'- TG GAA AGC TGA GAT GGA GGG CGG CAT -3' (FRAG 334) (SEQ. ID NO: 344)
     5'- TG GAA AGC TGA GAT GGA GGG CGG CA-3' (FRAG 335) (SEO. ID NO: 345)
     5'- TG GAA AGC TGA GAT GGA GGG CGG C-3' (FRAG 336) (SEO. ID NO: 346)
     5'- TG GAA AGC TGA GAT GGA GGG CGG -3' (FRAG 337) (SEO. ID NO: 347)
     5'- TG GAA AGC TGA GAT GGA GGG CG -3' (FRAG 338) (SEQ. ID NO: 348)
     5'- TG GAA AGC TGA GAT GGA GGG C -3' (FRAG 339) (SEQ. ID NO: 349)
     5'- TG GAA AGC TGA GAT GGA GGG -3' (FRAG 340) (SEQ. ID NO: 350)
     5'- TG GAA AGC TGA GAT GGA GG -3' (FRAG 341) (SEQ. ID NO: 351)
     5'- TG GAA AGC TGA GAT GGA G -3' (FRAG 342) (SEQ. ID NO: 352)
     5'- TG GAA AGC TGA GAT GGA -3' (FRAG 343) (SEQ. ID NO: 353)
     5'- TG GAA AGC TGA GAT GG -3' (FRAG 344) (SEQ. ID NO: 354)
     5'- TG GAA AGC TGA GAT G -3' (FRAG 345) (SEQ. ID NO: 355)
     5'- TG GAA AGC TGA GAT -3' (FRAG 346) (SEQ. ID NO: 356)
     5'- TG GAA AGC TGA GA-3' (FRAG 347) (SEQ. ID NO: 357)
     5'- TG GAA AGC TGA G-3' (FRAG 348) (SEQ. ID NO: 358)
     5'- TG GAA AGC TGA 3' (FRAG 349) (SEQ. ID NO: 359)
     5'- TG GAA AGC TG-3 (FRAG 350) (SEQ. ID NO: 360)
     5'- G GAA AGC TGA CAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 351) (SEO. ID NO: 361)
     5'- G GAA AGC TGA CAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 352) (SEQ. ID NO: 362)
     5'- G GAA AGC TGA CAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 353) (SEQ. ID NO: 363)
     5'- G GAA AGC TGA CAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 354) (SEQ. ID NO: 364)
     5'- G GAA AGC TGA CAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 355) (SEQ. ID NO: 365)
     5'- G GAA AGC TGA CAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 356) (SEQ. ID NO: 366)
    5'- G GAA AGC TGA CAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 357) (SEO. ID NO: 367)
     5'- G GAA AGC TGA C AT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 358) (SEQ. ID NO: 368)
     5'- G GAA AGC TGA CAT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 359) (SEQ. ID NO: 369)
     5'- G GAA AGC TGA CAT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 360) (SEQ. ID NO: 370)
     5'- G GAA AGC TGA CAT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 361) (SEQ. ID NO: 371)
    5'- G GAA AGC TGA CAT GGA GGG CGG CAT GGC GGG C-3' (FRAG 362) (SEQ. ID NO: 372)
     5'- G GAA AGC TGA CAT GGA GGG CGG CAT GGC GGG -3' (FRAG 363) (SEQ. ID NO: 373)
     5'- G GAA AGC TGA CAT GGA GGG CGG CAT GGC GG-3' (FRAG 364) (SEQ. ID NO: 374)
     5'- G GAA AGC TGA CAT GGA GGG CGG CAT GGC G-3' (FRAG 365) (SEQ. ID NO: 375)
     5'- G GAA AGC TGA CAT GGA GGG CGG CAT GGC -3' (FRAG 366) (SEQ. ID NO: 376)
     5^{\circ}\text{--} G GAA AGC TGA CAT GGA GGG CGG CAT GG -3^{\circ} (FRAG 367) (SEQ. ID NO: 377)
     5'- G GAA AGC TGA CAT GGA GGG CGG CAT G -3' (FRAG 368) (SEQ. ID NO: 378)
     5'- G GAA AGC TGA CAT GGA GGG CGG CAT -3' (FRAG 369) (SEQ. ID NO: 379)
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- 5'- G GAA AGC TGA (AT GGA GGG CGG CA-3' (FRAG 370) (SEO. ID NO: 380)
- 5'- G GAA AGC TGA (AT GGA GGG CGG C-3' (FRAG 371) (SEQ. ID NO: 381)
- 5'- G GAA AGC TGA GAT GGA GGG CGG -3' (FRAG 372) (SEQ. ID NO: 382)
- 5'- G GAA AGC TGA GAT GGA GGG CG -3' (FRAG 373) (SEQ. ID NO: 383)
- 5'- G GAA AGC TGA GAT GGA GGG C -3' (FRAG 374) (SEQ. ID NO: 384)
  - 5'- G GAA AGC TGA GAT GGA GGG -3' (FRAG 375) (SEQ. ID NO: 385)
  - 5'- G GAA AGC TGA GAT GGA GG -3' (FRAG 376) (SEQ. ID NO: 386)
  - 5'- G GAA AGC TGA (AT GGA G -3' (FRAG 377) (SEQ. ID NO: 387)
  - 5'- G GAA AGC TGA GAT GGA -3' (FRAG 378) (SEQ. ID NO: 388)
- 10 5'- G GAA AGC TGA ('AT GG -3' (FRAG 379) (SEQ. ID NO: 389)
  - 5'- G GAA AGC TGA (¡AT G -3' (FRAG 380) (SEQ. ID NO: 390)
  - 5'- G GAA AGC TGA (AT -3' (FRAG 381) (SEQ. ID NO: 391)
  - 5'- G GAA AGC TGA (¡A-3' (FRAG 382) (SEQ. ID NO: 392)
  - 5'- G GAA AGC TGA (1-3' (FRAG 383) (SEQ. ID NO: 393)
- 15 5'- G GAA AGC TGA-3' (FRAG 384) (SEQ. ID NO: 394)
  - 5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 385) (SEQ. ID NO: 395)
  - 5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 386) (SEQ. ID NO: 396)
  - 5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 387) (SEQ. ID NO: 397)
  - 5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 388) (SEQ. ID NO: 398)
- 20 5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 389) (SEQ. ID NO: 399)
  - 5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 390) (SEQ. ID NO: 400)
    5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 391) (SEQ. ID NO: 401)
  - 5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 392) (SEQ. ID NO: 402)
  - 5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 392) (SEQ. ID NO: 402)
- 25 5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 394) (SEQ. ID NO: 404)
  - 5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 395) (SEQ. ID NO: 405)
  - 5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG C-3' (FRAG 396) (SEQ. ID NO: 406)
  - 5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG -3' (FRAG 397) (SEQ. ID NO: 407)
- 5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GG-3' (FRAG 398) (SEQ. ID NO: 408)
  5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC G-3' (FRAG 399) (SEQ. ID NO: 409)
  - 5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC -3' (FRAG 400) (SEQ. ID NO: 410)
  - 5'- GAA AGC TGA GAT GGA GGG CGG CAT GG -3' (FRAG 401) (SEQ. ID NO: 411)
  - 5'- GAA AGC TGA GAT GGA GGG CGG CAT G -3' (FRAG 402) (SEQ. ID NO: 412)
  - 5'- GAA AGC TGA GAT GGA GGG CGG CAT -3' (FRAG 403) (SEQ. ID NO: 413)
- 35 5'- GAA AGC TGA GAT GGA GGG CGG CA-3' (FRAG 404) (SEQ. ID NO: 414)
  - 5'- GAA AGC TGA GAT GGA GGG CGG C-3' (FRAG 405) (SEQ. ID NO: 415)
  - 5'- GAA AGC TGA GAT GGA GGG CGG -3' (FRAG 406) (SEQ. ID NO: 416)
  - 5'- GAA AGC TGA GAT GGA GGG CG -3' (FRAG 407) (SEQ. ID NO: 417) 5'- GAA AGC TGA GAT GGA GGG C -3' (FRAG 408) (SEQ. ID NO: 418)
- 40 5'- GAA AGC TGA GAT GGA GGG -3' (FRAG 409) (SEQ. ID NO: 419)
  - 5'- GAA AGC TGA GAT GGA GG -3' (FRAG 410) (SEQ. ID NO: 420)
  - 5'- GAA AGC TGA GAT GGA G -3' (FRAG 411) (SEQ. ID NO: 421)
  - 5'- GAA AGC TGA GAT GGA -3' (FRAG 412) (SEQ. ID NO: 422)
  - 5'- GAA AGC TGA GAT GG -3' (FRAG 413) (SEQ. ID NO: 423)
- 45 5'- GAA AGC TGA GAT G -3' (FRAG 414) (SEQ. ID NO: 424)
  - 5'- GAA AGC TGA GAT -3' (FRAG 415) (SEQ. ID NO: 425)
  - 5'- GAA AGC TGA GA-3' (FRAG 416) (SEQ. ID NO: 426)
  - 5'- GAA AGC TGA G-3' (FRAG 417) (SEQ. ID NO: 427)
  - 5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 418) (SEQ. ID NO: 428)
- 50 5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 419) (SEQ. ID NO: 429)
  - 5'- AA AGC TGA GAI GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 420) (SEQ. ID NO: 430)
  - 5'- AA AGC TGA GAI GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 421) (SEQ. ID NO: 431)
  - 5'- AA AGC TGA GA1 GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 422) (SEQ. ID NO: 432)
  - 5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 423) (SEQ. ID NO: 433) 5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 424) (SEQ. ID NO: 434)
  - 5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3 (FRAG 424) (SEQ. ID NO: 434)
    5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 425) (SEQ. ID NO: 435)
  - 5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 426) (SEQ. ID NO: 436)
  - 5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 427) (SEQ. ID NO: 437)
  - 5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 428) (SEQ. ID NO: 438)
  - 5'- AA AGC TGA GAI GGA GGG CGG CAT GGC GGG C-3' (FRAG 429) (SEQ. ID NO: 439)
    5'- AA AGC TGA GAI GGA GGG CGG CAT GGC GGG -3' (FRAG 430) (SEO. ID NO: 440)
    - 5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GG-3' (FRAG 431) (SEQ. ID NO: 441)

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- 5'- AA AGC TGA GAT GGA GGG CGG CAT GGC G-3' (FRAG 432) (SEO. ID NO: 442)
- 5'- AA AGC TGA GAT' GGA GGG CGG CAT GGC -3' (FRAG 433) (SEO. ID NO: 443)
- 5'- AA AGC TGA GAT' GGA GGG CGG CAT GG -3' (FRAG 434) (SEQ. ID NO: 444)
- 5'- AA AGC TGA GAT GGA GGG CGG CAT G -3' (FRAG 435) (SEQ. ID NO: 445)
- 5'- AA AGC TGA GAT GGA GGG CGG CAT -3' (FRAG 436) (SEQ. ID NO: 446)
  - 5'- AA AGC TGA GA7' GGA GGG CGG CA-3' (FRAG 437) (SEQ. ID NO: 447)
  - 5'- AA AGC TGA GAI' GGA GGG CGG C-3' (FRAG 438) (SEQ. ID NO: 448)
  - 5'- AA AGC TGA GAT GGA GGG CGG -3' (FRAG 439) (SEQ. ID NO: 449)
  - 5'- AA AGC TGA GAT GGA GGG CG -3' (FRAG 440) (SEQ. ID NO: 450)
- 10 5'- AA AGC TGA GA1' GGA GGG C -3' (FRAG 441) (SEQ. ID NO: 451)
  - 5'- AA AGC TGA GAT GGA GGG -3' (FRAG 442) (SEQ. ID NO: 452)
  - 5'- AA AGC TGA GAT GGA GG -3' (FRAG 443) (SEQ. ID NO: 453)
  - 5'- AA AGC TGA GAT GGA G -3' (FRAG 444) (SEQ. ID NO: 454)
  - 5'- AA AGC TGA GAT GGA -3' (FRAG 445) (SEQ. ID NO: 455)
- 5'- AA AGC TGA GAT GG -3' (FRAG 446) (SEQ. ID NO: 456)
  - 5'- AA AGC TGA GAT G -3' (FRAG 447) (SEQ. ID NO: 457)
  - 5'- AA AGC TGA GAT'-3' (FRAG 448) (SEQ. ID NO: 458)
  - 5'- AA AGC TGA GA-3' (FRAG 449) (SEQ. ID NO: 459)
- 5'- A AGC TGA GAT GGA GGG CG G CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 450) (SEQ. ID NO: 460)
- 20 5'- A AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 451) (SEQ. ID NO: 461)
  - 5'- A AGC TGA GAT 'GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 452) (SEQ. ID NO: 462)
    - 5'- A AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 453) (SEQ. ID NO: 463)

    - 5'- A AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 454) (SEQ. ID NO: 464)
  - 5'- A AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 455) (SEQ. ID NO: 465)
- 5'- A AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 456) (SEQ. ID NO: 466)
  - 5'- A AGC TGA GAT 13GA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 457) (SEQ. ID NO: 467)
    - 5'- A AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 458) (SEQ. ID NO: 468)
    - 5'- A AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 459) (SEQ. ID NO: 469)
- 5'- A AGC TGA GAT 13GA GGG CGG CAT GGC GGG CA-3' (FRAG 460) (SEQ. ID NO: 470) 30
- 5'- A AGC TGA GAT GGA GGG CGG CAT GGC GGG C-3' (FRAG 461) (SEQ. ID NO: 471)
  - 5'- A AGC TGA GAT GGA GGG CGG CAT GGC GGG -3' (FRAG 462) (SEO. ID NO: 472)
  - 5'- A AGC TGA GAT (GGA GGG CGG CAT GGC GG-3' (FRAG 463) (SEQ. ID NO: 473) 5'- A AGC TGA GAT GGA GGG CGG CAT GGC G-3' (FRAG 464) (SEO. ID NO: 474)
  - 5'- A AGC TGA GAT GGA GGG CGG CAT GGC -3' (FRAG 465) (SEQ. ID NO: 475)
  - 5'- A AGC TGA GAT (3GA GGG CGG CAT GG -3' (FRAG 466) (SEQ. ID NO: 476)
    - 5'- A AGC TGA GAT GGA GGG CGG CAT G -3' (FRAG 467) (SEQ. ID NO: 477)
    - 5'- A AGC TGA GAT GGA GGG CGG CAT -3' (FRAG 468) (SEQ. ID NO: 478)
    - 5'- A AGC TGA GAT GGA GGG CGG CA-3' (FRAG 469) (SEQ. ID NO: 479)
  - 5'- A AGC TGA GAT GGA GGG CGG C-3' (FRAG 470) (SEQ. ID NO: 480)
- 40 5'- A AGC TGA GAT GGA GGG CGG -3' (FRAG 471) (SEQ. ID NO: 481)
  - 5'- A AGC TGA GAT (GGA GGG CG -3' (FRAG 472) (SEQ. ID NO: 482)
  - 5'- A AGC TGA GAT (3GA GGG C -3' (FRAG 473) (SEQ. ID NO: 483)
  - 5'- A AGC TGA GAT (3GA GGG -3' (FRAG 474) (SEO. ID NO: 484)
  - 5'- A AGC TGA GAT (3GA GG -3' (FRAG 475) (SEQ. ID NO: 485)
- 45 5'- A AGC TGA GAT GGA G -3' (FRAG 476) (SEQ. ID NO: 486)
  - 5'- A AGC TGA GAT (GGA -3' (FRAG 477) (SEQ. ID NO: 487)
  - 5'- A AGC TGA GAT (GG -3' (FRAG 478) (SEQ. ID NO: 488)
  - 5'- A AGC TGA GAT (3 -3' (FRAG 479) (SEQ. ID NO: 489)
  - 5'- A AGC TGA GAT · 3' (FRAG 480) (SEQ. ID NO: 490)
- 5'- AGC TGA GAT GIJA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 481) (SEQ. ID NO: 491)
  - 5'- AGC TGA GAT GJA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 482) (SEQ. ID NO: 492)
  - AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 483) (SEQ. ID NO: 493)
  - AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 484) (SEO. ID NO: 494) AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 485) (SEQ. ID NO: 495)
  - 5'- AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 486) (SEQ. ID NO: 496)
    - 5'- AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 487) (SEQ. ID NO: 497)
    - 5'- AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 488) (SEQ. ID NO: 498)
    - 5'- AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 489) (SEQ. ID NO: 499) 5'- AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 490) (SEQ. ID NO: 500)
  - 5'- AGC TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 491) (SEQ. ID NO: 501)
  - 5'- AGC TGA GAT GGA GGG CGG CAT GGC GGG C-3' (FRAG 492) (SEQ. ID NO: 502)
  - 5'- AGC TGA GAT GGA GGG CGG CAT GGC GGG -3' (FRAG 493) (SEQ. ID NO: 503)



- AGC TGA GAT GGA GGG CGG CAT GGC GG-3' (FRAG 494) (SEO. ID NO: 504)
- 5'- AGC TGA GAT G'3A GGG CGG CAT GGC G-3' (FRAG 495) (SEO. ID NO: 505)
- 5'- AGC TGA GAT GGA GGG CGG CAT GGC -3' (FRAG 496) (SEQ. ID NO: 506)
- 5'- AGC TGA GAT G'GA GGG CGG CAT GG -3' (FRAG 497) (SEQ. ID NO: 507)
- 5'- AGC TGA GAT GGA GGG CGG CAT G -3' (FRAG 498) (SEQ. ID NO: 508)
- 5'- AGC TGA GAT GGA GGG CGG CAT -3' (FRAG 499) (SEQ. ID NO: 509)
- 5'- AGC TGA GAT GGA GGG CGG CA-3' (FRAG 500) (SEQ. ID NO: 510)
- 5'- AGC TGA GAT GGA GGG CGG C-3' (FRAG 501) (SEQ. ID NO: 511)
- 5'- AGC TGA GAT GGA GGG CGG -3' (FRAG 502) (SEQ. ID NO: 512)
- 10 5'- AGC TGA GAT GGA GGG CG -3' (FRAG 503) (SEQ. ID NO: 513)
  - 5'- AGC TGA GAT GGA GGG C -3' (FRAG 504) (SEQ. ID NO: 514)
  - 5'- AGC TGA GAT GGA GGG -3' (FRAG 505) (SEQ. ID NO: 515)

  - 5'- AGC TGA GAT GGA GG -3' (FRAG 506) (SEQ. ID NO: 516) 5'- AGC TGA GAT GGA G -3' (FRAG 507) (SEQ. ID NO: 517)
- 15 5'- AGC TGA GAT GGA -3' (FRAG 508) (SEQ. ID NO: 518)
- - 5'- AGC TGA GAT GG -3' (FRAG 509) (SEQ. ID NO: 519) 5'- AGC TGA GAT G -3' (FRAG 510) (SEQ. ID NO: 520)
  - 5'- GC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 511) (SEQ. ID NO: 521)
  - 5'- GC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 512) (SEQ. ID NO: 522)
- 5'- GC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 513) (SEQ. ID NO: 523) 20
  - 5'- GC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 514) (SEQ. ID NO: 524)
  - 5'- GC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 515) (SEQ. ID NO: 525)
  - 5'- GC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 516) (SEQ. ID NO: 526)
  - 5'- GC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 517) (SEQ. ID NO: 527)
- 25 5'- GC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 518) (SEQ. ID NO: 528)
  - 5'- GC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 519) (SEQ. ID NO: 529)
    - 5'- GC TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 520) (SEQ. ID NO: 530)
    - 5'- GC TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 521) (SEQ. ID NO: 531)
    - GC TGA GAT GGA GGG CGG CAT GGC GGG C-3' (FRAG 522) (SEQ. ID NO: 532)
- 30 GC TGA GAT GGA GGG CGG CAT GGC GGG -3' (FRAG 523) (SEQ. ID NO: 533)
  - GC TGA GAT GGA GGG CGG CAT GGC GG-3' (FRAG 524) (SEQ. ID NO: 534)
  - 5'- GC TGA GAT GGA GGG CGG CAT GGC G-3' (FRAG 525) (SEQ. ID NO: 535)
  - 5'- GC TGA GAT GGA GGG CGG CAT GGC -3' (FRAG 526) (SEQ. ID NO: 536)
  - 5'- GC TGA GAT GGA GGG CGG CAT GG -3' (FRAG 527) (SEQ. ID NO: 537) 5'- GC TGA GAT GGA GGG CGG CAT G -3' (FRAG 528) (SEQ. ID NO: 538)
  - 5'- GC TGA GAT GGA GGG CGG CAT -3' (FRAG 529) (SEQ. ID NO: 539)
  - 5'- GC TGA GAT GGA GGG CGG CA-3' (FRAG 530) (SEQ. ID NO: 540)
  - 5'- GC TGA GAT GGA GGG CGG C-3' (FRAG 531) (SEQ. ID NO: 541)
  - 5'- GC TGA GAT GGA GGG CGG -3' (FRAG 532) (SEQ. ID NO: 542)
- 40 5'- GC TGA GAT GGA GGG CG -3' (FRAG 533) (SEQ. ID NO: 543)
  - 5'- GC TGA GAT GGA GGG C -3' (FRAG 534) (SEQ. ID NO: 544)
  - 5'- GC TGA GAT GGA GGG -3' (FRAG 535) (SEQ. ID NO: 545) 5'-
  - GC TGA GAT GGA GG -3' (FRAG 536) (SEQ. ID NO: 546) 5'-
  - GC TGA GAT GGA G  $\,$  -3' (FRAG 537) (SEQ. ID NO: 547) GC TGA GAT GGA -3' (FRAG 538) (SEQ. ID NO: 548)
  - GC TGA GAT GG -3' (FRAG 539) (SEQ. ID NO: 549)
    - C TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 540) (SEQ. ID NO: 550)
    - C TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 541) (SEQ. ID NO: 551)
- C TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 542) (SEQ. ID NO: 552) 50
- C TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 543) (SEQ. ID NO: 553)
  - C TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 544) (SEQ. ID NO: 554)
  - C TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 545) (SEQ. ID NO: 555) C TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 546) (SEQ. ID NO: 556)
  - 5'- C TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 547) (SEQ. ID NO: 557)
- 55 5'- C TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 548) (SEQ. ID NO: 558)
  - 5'- C TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 549) (SEQ. ID NO: 559)
  - 5'- C TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 550) (SEQ. ID NO: 560)
  - 5'- C TGA GAT GGA GGG CGG CAT GGC GGG C-3' (FRAG 551) (SEQ. ID NO: 561) 5'- C TGA GAT GGA GGG CGG CAT GGC GGG -3' (FRAG 552) (SEQ. ID NO: 562)
- 60 5'- C TGA GAT GGA GGG CGG CAT GGC GG-3' (FRAG 553) (SEQ. ID NO: 563)
  - 5'- C TGA GAT GGA GGG CGG CAT GGC G-3' (FRAG 554) (SEQ. ID NO: 564)
  - 5'- C TGA GAT GGA GGG CGG CAT GGC -3' (FRAG 555) (SEQ. ID NO: 565)

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- 5'- C TGA GAT GGA GGG CGG CAT GG -3' (FRAG 556) (SEQ. ID NO: 566)
- 5'- C TGA GAT GGA GGG CGG CAT G -3' (FRAG 557) (SEQ. ID NO: 567)
- 5'- C TGA GAT GGA GGG CGG CAT -3' (FRAG 558) (SEO. ID NO: 568)
- 5'- C TGA GAT GGA GGG CGG CA-3' (FRAG 559) (SEQ. ID NO: 569)
- 5'- C TGA GAT GGA GGG CGG C-3' (FRAG 560) (SEQ. ID NO: 570)
  - 5'- C TGA GAT GGA GGG CGG -3' (FRAG 561) (SEQ. ID NO: 571)
  - 5'- C TGA GAT GGA GGG CG -3' (FRAG 562) (SEQ. ID NO: 572)
  - 5'- C TGA GAT GGA GGG C -3' (FRAG 563) (SEQ. ID NO: 573)
  - 5'- C TGA GAT GGA GGG -3' (FRAG 564) (SEQ. ID NO: 574)
- 10 5'- C TGA GAT GGA GG -3' (FRAG 565) (SEQ. ID NO: 575)
  - 5'- C TGA GAT GGA G -3' (FRAG 566) (SEQ. ID NO: 576)
    - 5'- C'TGA GAT GGA -3' (FRAG 567) (SEQ. ID NO: 577)
    - 5'- TGA GAT GGA CGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 568) (SEQ. ID NO: 578)
  - 5'- TGA GAT GGA CGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 569) (SEQ. ID NO: 579)
- 15 5'- TGA GAT GGA CGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 570) (SEO. ID NO: 580)
  - 5'- TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 571) (SEQ. ID NO: 581)
  - 5'- TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 572) (SEQ. ID NO: 582) 5'- TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 573) (SEQ. ID NO: 583)
  - 5'- TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 574) (SEQ. ID NO: 584)
- 20 5'- TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 575) (SEQ. ID NO: 585)
  - 5'- TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 576) (SEQ. ID NO: 586)
    - 5'- TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 577) (SEQ. ID NO: 587)
    - 5'- TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 578) (SEQ. ID NO: 588)
    - 5'- TGA GAT GGA GGG CGG CAT GGC GGG C-3' (FRAG 579) (SEQ. ID NO: 589)
- 25 5'- TGA GAT GGA GGG CGG CAT GGC GGG -3' (FRAG 580) (SEQ. ID NO: 590)
  - 5'- TGA GAT GGA GGG CGG CAT GGC GG-3' (FRAG 581) (SEQ. ID NO: 591)
    - 5'- TGA GAT GGA GGG CGG CAT GGC G-3' (FRAG 582) (SEQ. ID NO: 592)
    - 5'- TGA GAT GGA GGG CGG CAT GGC -3' (FRAG 583) (SEQ. ID NO: 593)
    - 5'- TGA GAT GGA GGG CGG CAT GGC -3' (FRAG 584) (SEQ. ID NO: 594)
    - 5'- TGA GAT GGA GGG CGG CAT G -3' (FRAG 585) (SEQ. ID NO: 595)
    - 5'- TGA GAT GGA GGG CGG CAT -3' (FRAG 586) (SEQ. ID NO: 596)
    - 5'- TGA GAT GGA GGG CGG CA-3' (FRAG 587) (SEQ. ID NO: 597)
    - 5'- TGA GAT GGA GGG CGG C-3' (FRAG 588) (SEQ. ID NO: 598)
    - 5'- TGA GAT GGA GGG CGG -3' (FRAG 589) (SEQ. ID NO: 599)
- 35 5'- TGA GAT GGA GGG CG -3' (FRAG 590) (SEQ. ID NO: 600)
  - 5'- TGA GAT GGA GGG C -3' (FRAG 591) (SEQ. ID NO: 601)
  - 5'- TGA GAT GGA GGG -3' (FRAG 592) (SEQ. ID NO: 602)
  - 5'- TGA GAT GGA GG -3' (FRAG 593) (SEQ. ID NO: 603) 5'- TGA GAT GGA G -3' (FRAG 594) (SEQ. ID NO: 604)
- 40 5'- GA GAT GGA GC G CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 595) (SEQ. ID NO: 605)
  - 5'- GA GAT GGA GC G CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 596) (SEQ. ID NO: 606)
  - 5'- GA GAT GGA GC G CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 597) (SEQ. ID NO: 607)
  - 5'- GA GAT GGA GC G CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 598) (SEQ. ID NO: 608)
  - 5'- GA GAT GGA GC G CGG CAT GGC GGG CAC AGG CT-3' (FRAG 599) (SEQ. ID NO: 609)
  - 5'- GA GAT GGA GC GCGC CAT GGC GGG CAC AGG C-3' (FRAG 601) (SEQ. ID NO: 610)
    5'- GA GAT GGA GC GCGC CAT GGC GGG CAC AGG -3' (FRAG 601) (SEQ. ID NO: 611)
  - 5'- GA GAT GGA GC G CGG CAT GGC GGG CAC AGG -3' (FRAG 601) (SEQ. ID NO: 611)
    5'- GA GAT GGA GC G CGG CAT GGC GGG CAC AG-3' (FRAG 602) (SEQ. ID NO: 612)
  - 5'- GA GAT GGA GC G CGG CAT GGC GGG CAC A-3' (FRAG 603) (SEQ. ID NO: 613)
- 5'- GA GAT GGA GC G CGG CAT GGC GGG CA-3' (FRAG 604) (SEQ. ID NO: 614)
  50 5'- GA GAT GGA GC G CGG CAT GGC GGG CA-3' (FRAG 605) (SEQ. ID NO: 615)
  - 5'- GA GAT GGA GC G CGG CAT GGC GGG CA3' (FRAG 605) (SEQ. ID NO: 615)
    5'- GA GAT GGA GC G CGG CAT GGC GGG C-3' (FRAG 606) (SEQ. ID NO: 616)
    - 5'- GA GAT GGA GC G CGG CAT GGC GGG C-3' (FRAG 606) (SEQ. ID NO: 616)
      5'- GA GAT GGA GC G CGG CAT GGC GGG -3' (FRAG 607) (SEQ. ID NO: 617)
    - 5'- GA GAT GGA GC G CGG CAT GGC GG-3' (FRAG 608) (SEQ. ID NO: 618)
  - 5'- GA GAT GGA GC G CGG CAT GGC G-3' (FRAG 609) (SEQ. ID NO: 619)
- 55 5'- GA GAT GGA GC G CGG CAT GGC -3' (FRAG 610) (SEQ. ID NO: 620)
  - 5'- GA GAT GGA GC G CGG CAT GG -3' (FRAG 611) (SEQ. ID NO: 621)
  - 5'- GA GAT GGA GCG CGG CAT G -3' (FRAG 612) (SEQ. ID NO: 622)
  - 5'- GA GAT GGA GCG CGG CAT -3' (FRAG 613) (SEQ. ID NO: 623) 5'- GA GAT GGA GCG CGG CA-3' (FRAG 614) (SEQ. ID NO: 624)
  - 5'- GA GAT GGA GCG CGG C-3' (FRAG 615) (SEQ. ID NO: 625)
    - 5'- GA GAT GGA GCG CGG -3' (FRAG 616) (SEQ. ID NO: 626)
    - 5'- GA GAT GGA GC G CG -3' (FRAG 617) (SEQ. ID NO: 627)



- GA GAT GGA GCG C -3' (FRAG 618) (SEQ. ID NO: 628)
- 5'-GA GAT GGA GCG -3' (FRAG 619) (SEQ. ID NO: 629)
- 5'-GA GAT GGA GC: -3' (FRAG 620) (SEQ. ID NO: 630)
- 5'-A GAT GGA GGC CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 621) (SEQ. ID NO: 631)
  - 5'-A GAT GGA GGC CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 622) (SEQ. ID NO: 632)
    - 5'-A GAT-GGA GGC CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 623) (SEQ. ID NO: 633)
    - 5'-A GAT GGA GGC CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 624) (SEQ. ID NO: 634)
    - 5'-A GAT GGA GGC CGG CAT GGC GGG CAC AGG CT-3' (FRAG 625) (SEQ. ID NO: 635)
- 5'-A GAT GGA GGC CGG CAT GGC GGG CAC AGG C-3' (FRAG 626) (SEQ. ID NO: 636) 10 5'-
- A GAT GGA GGC CGG CAT GGC GGG CAC AGG -3' (FRAG 627) (SEQ. ID NO: 637)
  - 5'-A GAT GGA GGC CGG CAT GGC GGG CAC AG-3' (FRAG 628) (SEQ. ID NO: 638) 5'-
  - A GAT GGA GGC CGG CAT GGC GGG CAC A-3' (FRAG 629) (SEQ. ID NO: 639)
  - 5'-A GAT GGA GGC CGG CAT GGC GGG CAC-3' (FRAG 630) (SEQ. ID NO: 640)
- 5'-A GAT GGA GGC CGG CAT GGC GGG CA-3' (FRAG 631) (SEQ. ID NO: 641) 15
  - A GAT GGA GGC CGG CAT GGC GGG C-3' (FRAG 632) (SEQ. ID NO: 642) 5'-
    - A GAT GGA GGC CGG CAT GGC GGG -3' (FRAG 633) (SEQ. ID NO: 643) 5'-
    - A GAT GGA GGC CGG CAT GGC GG-3' (FRAG 634) (SEQ. ID NO: 644) 5'-
    - A GAT GGA GGC CGG CAT GGC G-3' (FRAG 635) (SEQ. ID NO: 645) A GAT GGA GGC CGG CAT GGC -3' (FRAG 636) (SEQ. ID NO: 646)
- 20 51-
- A GAT GGA GGC CGG CAT GG -3' (FRAG 637) (SEQ. ID NO: 647)
- 5'-A GAT GGA GGC CGG CAT G -3' (FRAG 638) (SEQ. ID NO: 648)
  - 5'-A GAT GGA GGC CGG CAT -3' (FRAG 639) (SEQ. ID NO: 649)
  - 5'-A GAT GGA GGC CGG CA-3' (FRAG 640) (SEQ. ID NO: 650)
- 5'-A GAT GGA GGC CGG C-3' (FRAG 641) (SEQ. ID NO: 651)
- 25 A GAT GGA GGC CGG -3' (FRAG 642) (SEQ. ID NO: 652) 5'-
  - 5'-A GAT GGA GGC CG -3' (FRAG 643) (SEQ. ID NO: 653)
    - 5'-A GAT GGA GGC C -3' (FRAG 644) (SEQ. ID NO: 654)
  - 5'-A GAT GGA GGC -3' (FRAG 645) (SEQ. ID NO: 655)
- GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 646) (SEQ. ID NO: 656) 5'-
- 30 5'-GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 647) (SEQ. ID NO: 657)
- GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 648) (SEQ. ID NO: 658) 5'-
  - GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 6) (SEQ. ID NO: 659) 5'-
  - 5'-GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 650) (SEO. ID NO: 660)
  - 5'-GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 651) (SEQ. ID NO: 661)
  - 5'-GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 652) (SEQ. ID NO: 662) 5'-GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 653) (SEQ. ID NO: 663)
  - 5'-GAT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 654) (SEQ. ID NO: 664)
  - 5'-GAT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 655) (SEQ. ID NO: 665)
  - 5'-GAT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 656) (SEQ. ID NO: 666)
- 40 5'-GAT GGA GGG CGG CAT GGC GGG C-3' (FRAG 657) (SEQ. ID NO: 667)
  - 5'-GAT GGA GGG CGG CAT GGC GGG -3' (FRAG 658) (SEQ. ID NO: 668) 5'-
  - GAT GGA GGG CGG CAT GGC GG-3' (FRAG 659) (SEQ. ID NO: 669) 5'-
  - GAT GGA GGG CGG CAT GGC G-3' (FRAG 660) (SEQ. ID NO: 670)
- 5'-GAT GGA GGG CGG CAT GGC -3' (FRAG 661) (SEQ. ID NO: 671) 45 5'-GAT GGA GGG CGG CAT GG -3' (FRAG 662) (SEQ. ID NO: 672)
  - 5'-GAT GGA GGG CGG CAT G -3' (FRAG 663) (SEQ. ID NO: 673)
  - 5'-GAT GGA GGG CGG CAT -3' (FRAG 664) (SEQ. ID NO: 674)
  - 5'-GAT GGA GGG (CGG CA-3' (FRAG 665) (SEQ. ID NO: 675)
  - GAT GGA GGG CGG C-3' (FRAG 666) (SEQ. ID NO: 676)
- 50 5'-GAT GGA GGG CGG -3' (FRAG 667) (SEQ. ID NO: 677)
  - 5'-GAT GGA GGG CG -3' (FRAG 668) (SEQ. ID NO: 678)
  - 5'-GAT GGA GGG (C -3' (FRAG 669) (SEQ. ID NO: 679)
  - 5'-AT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 670) (SEO. ID NO: 680)
  - 5'-AT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 671) (SEQ. ID NO: 681)
- 55 5'-AT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 672) (SEQ. ID NO: 682)
  - 5'-AT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 673) (SEQ. ID NO: 683)
  - 5'-AT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 674) (SEQ. ID NO: 684) 5'-
  - AT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 675) (SEQ. ID NO: 685) 51-AT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 676) (SEQ. ID NO: 686)
- 5'-60 AT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 677) (SEQ. ID NO: 687)
  - 5'-AT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 678) (SEQ. ID NO: 688)
  - AT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 679) (SEQ. ID NO: 689)

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- 5'- AT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 680) (SEQ. ID NO: 690)
- 5'- AT GGA GGG CGG CAT GGC GGG C-3' (FRAG 681) (SEQ. ID NO: 691)
- 5'- AT GGA GGG CGG CAT GGC GGG -3' (FRAG 682) (SEQ. ID NO: 692)
- 5'- AT GGA GGG CGG CAT GGC GG-3' (FRAG 683) (SEQ. ID NO: 693)
- 5'- AT GGA GGG CGG CAT GGC G-3' (FRAG 684) (SEQ. ID NO: 694)
  - 5'- AT GGA GGG CGG CAT GGC -3' (FRAG 685) (SEQ. ID NO: 695)
  - 5'- AT GGA GGG CGG CAT GG -3' (FRAG 686) (SEQ. ID NO: 696)
  - 5'- AT GGA GGG CGG CAT G -3' (FRAG 687) (SEQ. ID NO: 697)
- 5'- AT GGA GGG CGG CAT -3' (FRAG 688) (SEQ. ID NO: 698)
- 10 5'- AT GGA GGG CGG CA-3' (FRAG 689) (SEQ. ID NO: 699)
  - 5'- AT GGA GGG CGG C-3' (FRAG 690) (SEQ. ID NO: 700)
  - 5'- AT GGA GGG CGG -3' (FRAG 691) (SEQ. ID NO: 701)
  - 5'- AT GGA GGG CG -3' (FRAG 692) (SEQ. ID NO: 702)
  - 5'- T GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 693) (SEQ. ID NO: 703)
- 15 5'- T GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 694) (SEQ. ID NO: 704)
  - 5'- T GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 695) (SEQ. ID NO: 705)
  - 5'- T GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 696) (SEQ. ID NO: 706)
  - 5'- T GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 697) (SEQ. ID NO: 707)
  - 5'- T GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 698) (SEQ. ID NO: 708)
- 20 5'- T GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 699) (SEQ. ID NO: 709)
  - 5'- T GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 700) (SEQ. ID NO: 710)
    - 5'- T GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 701) (SEQ. ID NO: 711)
    - 5'- T GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 702) (SEQ. ID NO: 712)
    - 5'- T GGA GGG CGG CAT GGC GGG CA-3' (FRAG 703) (SEQ. ID NO: 713)
- 25 5'- T GGA GGG CGG CAT GGC GGG C-3' (FRAG 704) (SEQ. ID NO: 714)
  - 5'- T GGA GGG CGG CAT GGC GGG -3' (FRAG 705) (SEQ. ID NO: 715)
  - 5'- T GGA GGG CGG CAT GGC GG-3' (FRAG 706) (SEQ. ID NO: 716)
  - 5'- T GGA GGG CGG CAT GGC G-3' (FRAG 707) (SEQ. ID NO: 717)
  - 5'- T GGA GGG CGG CAT GGC -3' (FRAG 708) (SEQ. ID NO: 718)
- 30 5'- T GGA GGG CGG CAT GG -3' (FRAG 709) (SEQ. ID NO: 719)
  - 5'- T GGA GGG CGG CAT G -3' (FRAG 710) (SEQ. ID NO: 720)
  - 5'- T GGA GGG CGG CAT -3' (FRAG 711) (SEQ. ID NO: 721)
  - 5'- T GGA GGG CGG CA-3' (FRAG 712) (SEQ. ID NO: 722)
  - 5'- T GGA GGG CGG C-3' (FRAG 713) (SEQ. ID NO: 723)
  - 5'- T GGA GGG CGG: -3' (FRAG 714) (SEQ. ID NO: 724)
    5'- GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 715) (SEQ. ID NO: 725)
  - 5'- GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 716) (SEQ. ID NO: 726)
  - 5'- GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 717) (SEQ. ID NO: 727)
  - 5'- GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 718) (SEQ. ID NO: 728)
- 40 5'- GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 719) (SEQ. ID NO: 729)
  - 5'- GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 720) (SEQ. ID NO: 730)
  - 5'- GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 721) (SEQ. ID NO: 731) 5'- GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 722) (SEQ. ID NO: 732)
  - 5'- GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 723) (SEQ. ID NO: 733)
- 45 5'- GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 724) (SEQ. ID NO: 734)
  - 5'- GGA GGG CGG CAT GGC GGG CA-3' (FRAG 725) (SEQ. ID NO: 735)
  - 5'- GGA GGG CGG CAT GGC GGG C-3' (FRAG 726) (SEQ. ID NO: 736)
  - 5'- GGA GGG CGG CAT GGC GGG -3' (FRAG 727) (SEQ. ID NO: 737)
  - 5'- GGA GGG CGG CAT GGC GG-3' (FRAG 728) (SEQ. ID NO: 738) 5'- GGA GGG CGG CAT GGC G-3' (FRAG 729) (SEQ. ID NO: 739)
  - 5'- GGA GGG CGG CAT GGC -3' (FRAG 729) (SEQ. ID NO: 739)
    - 5'- GGA GGG CGG CAT GG -3' (FRAG 731) (SEQ. ID NO: 741)
    - 5'- GGA GGG CGG CAT G -3' (FRAG 732) (SEQ. ID NO: 742)
    - 5'- GGA GGG CGG CAT -3' (FRAG 733) (SEQ. ID NO: 743)
- 55 5'- GGA GGG CGG CA-3' (FRAG 734) (SEQ. ID NO: 744)
  - 5'- GGA GGG CGG C-3' (FRAG 735) (SEQ. ID NO: 745)
  - 5'- GA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 736) (SEQ. ID NO: 746)
  - 5'- GA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 737) (SEQ. ID NO: 747)
  - 5'- GA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 738) (SEQ. ID NO: 748)
- 60 5'- GA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 739) (SEQ. ID NO: 749)
  5'- GA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 740) (SEQ. ID NO: 750)
  - 5'- GA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 740) (SEQ. ID NO: 750) 5'- GA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 741) (SEQ. ID NO: 751)

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- 5'-GA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 742) (SEQ. ID NO: 752)
- 5'-GA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 743) (SEQ. ID NO: 753)
- 5'-GA GGG CGG CAT GGC GGG CAC A-3' (FRAG 744) (SEQ. ID NO: 754)
- 5'-GA GGG CGG CAT GGC GGG CAC-3' (FRAG 745) (SEQ. ID NO: 755)
- 5'-GA GGG CGG CAT GGC GGG CA-3' (FRAG 746) (SEQ. ID NO: 756)
- GA GGG CGG CAT GGC GGG C-3' (FRAG 747) (SEQ. ID NO: 757)
- 5'-GA GGG CGG CAT GGC GGG -3' (FRAG 748) (SEQ. ID NO: 758)
- 5'-GA GGG CGG CAT GGC GG-3' (FRAG 749) (SEQ. ID NO: 759)
- 5'-GA GGG CGG CAT GGC G-3' (FRAG 750) (SEQ. ID NO: 760)
- 10 5'-GA GGG CGG CAT GGC -3' (FRAG 751) (SEQ. ID NO: 761)
  - 5'-GA GGG CGG CAT GG -3' (FRAG 752) (SEQ. ID NO: 762)
  - 5'-GA GGG CGG CAT G -3' (FRAG 753) (SEQ. ID NO: 763)
  - 5'-
  - GA GGG CGG CAT -3' (FRAG 754) (SEQ. ID NO: 764) 5'-GA GGG CGG CA-3' (FRAG 755) (SEQ. ID NO: 765)
- 15 5'-A GGG CGG CA<sup>--</sup> GGC GGG CAC AGG CTG GGC-3' (FRAG 756) (SEQ. ID NO: 766)
  - 5'-A GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 757) (SEQ. ID NO: 767)
  - 5'-A GGG CGG CA" GGC GGG CAC AGG CTG G-3' (FRAG 758) (SEQ. ID NO: 768)
  - 5'-A GGG CGG CAC GGG CAC AGG CTG -3' (FRAG 759) (SEQ. ID NO: 769)
  - 5'-A GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 760) (SEQ. ID NO: 770)
- 20 5'-A GGG CGG CA' GGC GGG CAC AGG C-3' (FRAG 761) (SEQ. ID NO: 771)
- 5'-A GGG CGG CA<sup>--</sup> GGC GGG CAC AGG -3' (FRAG 762) (SEQ. ID NO: 772)
  - 5'-A GGG CGG CAC GGC GGG CAC AG-3' (FRAG 763) (SEQ. ID NO: 773)
  - A GGG CGG CA<sup>--</sup> GGC GGG CAC A-3' (FRAG 764) (SEQ. ID NO: 774) 5'-A GGG CGG CA<sup>--</sup> GGC GGG CAC-3' (FRAG 765) (SEQ. ID NO: 775) 5'-
- 25 51-A GGG CGG CA<sup>--</sup> GGC GGG CA-3' (FRAG 766) (SEQ. ID NO: 776)
- 5'-A GGG CGG CAT GGC GGG C-31 (FRAG 767) (SEQ. ID NO: 777)
  - A GGG CGG CA<sup>--</sup> GGC GGG -3' (FRAG 768) (SEQ. ID NO: 778) 51-
  - A GGG CGG CA<sup>--</sup> GGC GG-3' (FRAG 769) (SEQ. ID NO: 779) 5'-
  - 5'-A GGG CGG CA" GGC G-3' (FRAG 770) (SEQ. ID NO: 780)
- 30 5'-A GGG CGG CA<sup>^</sup> GGC -3' (FRAG 771) (SEQ. ID NO: 781)
  - 5'-A GGG CGG CA<sup>--</sup> GG -3' (FRAG 772) (SEQ. ID NO: 782)
  - 5'-A GGG CGG CA' G -3' (FRAG 773) (SEQ. ID NO: 783)
  - A GGG CGG CA" -3' (FRAG 774) (SEQ. ID NO: 784) 5'-
  - 5'-GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 775) (SEQ. ID NO: 785)
- 35 GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 776) (SEQ. ID NO: 786)
  - 5'-GGG CGG CAT 3GC GGG CAC AGG CTG G-3' (FRAG 777) (SEQ. ID NO: 787)
  - 5'-GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 778) (SEQ. ID NO: 788)
  - 5'-GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 779) (SEQ. ID NO: 789)
  - 5'-GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 780) (SEQ. ID NO: 790)
- 40 5'-GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 781) (SEQ. ID NO: 791)
  - 5'-GGG CGG CAT 3GC GGG CAC AG-3' (FRAG 782) (SEQ. ID NO: 792)
  - GGG CGG CAT 3GC GGG CAC A-3' (FRAG 783) (SEQ. ID NO: 793) 5'-
  - 5'-GGG CGG CAT GGC GGG CAC-3' (FRAG 784) (SEQ. ID NO: 794)
  - GGG CGG CAT 3GC GGG CA-3' (FRAG 785) (SEQ. ID NO: 795) 5'-51-
  - GGG CGG CAT GGC GGG C-3' (FRAG 786) (SEQ. ID NO: 796) 5'-GGG CGG CAT GGC GGG -3' (FRAG 787) (SEQ. ID NO: 797)
  - 5'-GGG CGG CAT 3GC GG-3' (FRAG 788) (SEQ. ID NO: 798)
  - 5'-GGG CGG CAT GGC G-3' (FRAG 789) (SEQ. ID NO: 799)
  - 5'-GGG CGG CAT 3GC -3' (FRAG 790) (SEQ. ID NO: 800)
- 50 GGG CGG CAT GG -3' (FRAG 791) (SEQ. ID NO: 801)
  - 5'-GGG CGG CAT 3 -3' (FRAG 792) (SEQ. ID NO: 802)
    - 5'-GG CGG CAT GGC GGG CAC AG G CTG GGC-3' (FRAG 793) (SEQ. ID NO: 803)
    - GG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 794) (SEQ. ID NO: 804) 5'-
    - 5'-GG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 795) (SEQ. ID NO: 805)
    - GG CGG CAT G3C GGG CAC AGG CTG -3' (FRAG 796) (SEQ. ID NO: 806)
    - 5'-GG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 797) (SEQ. ID NO: 807) GG CGG CAT GGC GGG CAC AGG C-3' (FRAG 798) (SEQ. ID NO: 808)
    - 5'-GG CGG CAT GGC GGG CAC AGG -3' (FRAG 799) (SEQ. ID NO: 809)
    - 5'-GG CGG CAT GGC GGG CAC AG-3' (FRAG 800) (SEQ. ID NO: 810)
- 60 5'-GG CGG CAT GGC GGG CAC A-3' (FRAG 801) (SEQ. ID NO: 811)
  - 5'-GG CGG CAT GGC GGG CAC-3' (FRAG 802) (SEQ. ID NO: 812)
  - 5'-GG CGG CAT GGC GGG CA-3' (FRAG 803) (SEQ. ID NO: 813)



GG CGG CAT GGC GGG C-3' (FRAG 804) (SEQ. ID NO: 814) 5'-5'-GG CGG CAT GGC GGG -3' (FRAG 805) (SEQ. ID NO: 815) 5'-GG CGG CAT GGC GG-3' (FRAG 806) (SEQ. ID NO: 816) 5'-GG CGG CAT GGC G-3' (FRAG 807) (SEQ. ID NO: 817) 5 5'-GG CGG CAT GGC -3' (FRAG 808) (SEQ. ID NO: 818) 5'-GG CGG CAT GG -3' (FRAG 809) (SEQ. ID NO: 819) 5'-G CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 810) (SEQ. ID NO: 820) 5'-G CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 811) (SEQ. ID NO: 821) 5'-G CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 812) (SEQ. ID NO: 822) 10 5'-G CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 813) (SEQ. ID NO: 823) G CGG CAT GGC GGG CAC AGG CT-3' (FRAG 814) (SEQ. ID NO: 824) 5'-5'-G CGG CAT GGC GGG CAC AGG C-3' (FRAG 815) (SEQ. ID NO: 825) 5'-G CGG CAT GGC GGG CAC AGG -3' (FRAG 816) (SEQ. ID NO: 826) 5'-G CGG CAT GGC GGG CAC AG-3' (FRAG 817) (SEQ. ID NO: 827) 15 5'-G CGG CAT GGC GGG CAC A-3' (FRAG 818) (SEQ. ID NO: 828) 5'-G CGG CAT GGC GGG CAC-3' (FRAG 819) (SEQ. ID NO: 829) 5'-G CGG CAT GGC GGG CA-3' (FRAG 820) (SEQ. ID NO: 830) 5'-G CGG CAT GGC GGG C-3' (FRAG 821) (SEQ. ID NO: 831) 5'-G CGG CAT GGC GGG -3' (FRAG 822) (SEQ. ID NO: 832) 20 5'-G CGG CAT GGC GG-3' (FRAG 823) (SEQ. ID NO: 833) 5'-G CGG CAT GGC G-3' (FRAG 824) (SEQ. ID NO: 834) G CGG CAT GGC -3' (FRAG 825) (SEQ. ID NO: 835) 5'-5'-CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 826) (SEQ. ID NO: 836) 5'-CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 827) (SEQ. ID NO: 837) 25 5'-CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 828) (SEQ. ID NO: 838) 5'-CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 829) (SEQ. ID NO: 839) 5'-CGG CAT GGC GGG CAC AGG CT-3' (FRAG 830) (SEQ. ID NO: 840) CGG CAT GGC GGG CAC AGG C-3' (FRAG 831) (SEQ. ID NO: 841) 5'-5'-CGG CAT GGC GGG CAC AGG -3' (FRAG 832) (SEQ. ID NO: 842) 30 5'-CGG CAT GGC GGG CAC AG-3' (FRAG 833) (SEQ. ID NO: 843) 5'-CGG CAT GGC GGG CAC A-3' (FRAG 834) (SEQ. ID NO: 844) CGG CAT GGC GGG CAC-3' (FRAG 835) (SEQ. ID NO: 845) 5'-5'-CGG CAT GGC GGG CA-3' (FRAG 836) (SEO. ID NO: 846) 5'-CGG CAT GGC GGG C-3' (FRAG 837) (SEO. ID NO: 847) 35 5'-CGG CAT GGC GGG -3' (FRAG 838) (SEQ. ID NO: 848) 5'-CGG CAT GGC GG-3' (FRAG 839) (SEQ. ID NO: 849) 5'-CGG CAT GGC G-3' (FRAG 840) (SEQ. ID NO: 850) 5'-GG CAT GGC GGG CAC AGG C TG GGC-3' (FRAG 841) (SEQ. ID NO: 851) 5'-GG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 842) (SEQ. ID NO: 852) 40 5'-GG CAT GGC CIGG CAC AGG CTG G-3' (FRAG 843) (SEQ. ID NO: 853) 5'-GG CAT GGC GGG CAC AGG CTG -3' (FRAG 844) (SEQ. ID NO: 854) 5'-GG CAT GGC GGG CAC AGG CT-3' (FRAG 845) (SEQ. ID NO: 855) 5'-GG CAT GGC GGG CAC AGG C-3' (FRAG 846) (SEQ. ID NO: 856) 5'-GG CAT GGC (iGG CAC AGG -3' (FRAG 847) (SEQ. ID NO: 857) 45 5'-GG CAT GGC CiGG CAC AG-3' (FRAG 848) (SEQ. ID NO: 858) 5'-GG CAT GGC GGG CAC A-3' (FRAG 849) (SEQ. ID NO: 859) 5'-GG CAT GGC GGG CAC-3' (FRAG 850) (SEQ. ID NO: 860) 5'-GG CAT GGC (GG CA-3' (FRAG 851) (SEQ. ID NO: 861) 5'-GG CAT GGC CiGG C-3' (FRAG 852) (SEQ. ID NO: 862) 50 5'-GG CAT GGC (GG -3' (FRAG 853) (SEO. ID NO: 863) 5'-GG CAT GGC (G-3' (FRAG 854) (SEQ. ID NO: 864) 5'-G CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 855) (SEO. ID NO: 865) 5'-G CAT GGC GGG CAC AGG CTG GG-3' (FRAG 856) (SEO. ID NO: 866) 5'-G CAT GGC GCiG CAC AGG CTG G-3' (FRAG 857) (SEQ. ID NO: 867) 55 5'-G CAT GGC GGG CAC AGG CTG -3' (FRAG 858) (SEQ. ID NO: 868) 5'-G CAT GGC GGG CAC AGG CT-3' (FRAG 859) (SEQ. ID NO: 869) 5'-G CAT GGC GGG CAC AGG C-3' (FRAG 860) (SEQ. ID NO: 870) 5'-G CAT GGC GCiG CAC AGG -3' (FRAG 861) (SEQ. ID NO: 871) 5'-G CAT GGC GGG CAC AG-3' (FRAG 862) (SEQ. ID NO: 872) 60 5'-G CAT GGC GGG CAC A-3' (FRAG 863) (SEQ. ID NO: 873) 5'-G CAT GGC GCG CAC-3' (FRAG 864) (SEQ. ID NO: 874)

G CAT GGC GGG CA-3' (FRAG 865) (SEQ. ID NO: 875)



5'-G CAT GGC GGG C-3' (FRAG 866) (SEQ. ID NO: 876) 5'-G CAT GGC GCiG -3' (FRAG 867) (SEQ. ID NO: 877) 5'-CAT GGC GGC CAC AGG CTG GGC-3' (FRAG 868) (SEQ. ID NO: 878) 5'-CAT GGC GGC; CAC AGG CTG GG-3' (FRAG 869) (SEQ. ID NO: 879) 5 5'-CAT GGC GGC CAC AGG CTG G-3' (FRAG 870) (SEQ. ID NO: 880) 5'-CAT GGC GGC CAC AGG CTG -3' (FRAG 871) (SEQ. ID NO: 881) 5'-CAT GGC GGC CAC AGG CT-3' (FRAG 872) (SEQ. ID NO: 882) 5'-CAT GGC GGC CAC AGG C-3' (FRAG 873) (SEQ. ID NO: 883) 5'-CAT GGC GGC CAC AGG -3' (FRAG 874) (SEQ. ID NO: 884) 10 5'-CAT GGC GGC CAC AG-3' (FRAG 875) (SEQ. ID NO: 885) 5'-CAT GGC GGC CAC A-3' (FRAG 876) (SEQ. ID NO: 886) 5'-CAT GGC GGC CAC-3' (FRAG 877) (SEQ. ID NO: 887) 5'-CAT GGC GGC CA-3' (FRAG 878) (SEQ. ID NO: 888) 5'-CAT GGC GGC C-3' (FRAG 879) (SEQ. ID NO: 889) 15 5'-AT GGC GGG CAC AGG CTG GGC-3' (FRAG 880) (SEQ. ID NO: 890) 5'-AT GGC GGG CAC AGG CTG GG-3' (FRAG 881) (SEQ. ID NO: 891) 5'-AT GGC GGG CAC AGG CTG G-3' (FRAG 882) (SEQ. ID NO: 892) AT GGC GGG CAC AGG CTG -3' (FRAG 883) (SEQ. ID NO: 893) 5'-5'-AT GGC GGG CAC AGG CT-3' (FRAG 884) (SEQ. ID NO: 894) 20 5'-AT GGC GGG CAC AGG C-3' (FRAG 885) (SEQ. ID NO: 895) 5'-AT GGC GGG CAC AGG -3' (FRAG 886) (SEQ. ID NO: 896) AT GGC GGG CAC AG-3' (FRAG 887) (SEQ. ID NO: 897) 5'-5'-AT GGC GGG CAC A-3' (FRAG 888) (SEQ. ID NO: 898) 5'-AT GGC GGG CAC-3' (FRAG 889) (SEQ. ID NO: 899) AT GGC GGG CA-3' (FRAG 890) (SEQ. ID NO: 900) 25 5'-T GGC GGG CAC AGG CTG GGC-3' (FRAG 891) (SEQ. ID NO: 901) 5'-T GGC GGG CAC AGG CTG GG-3' (FRAG 892) (SEQ. ID NO: 902) 5'-5'-T GGC GGG CAC AGG CTG G-3' (FRAG 893) (SEQ. ID NO: 903) T GGC GGG CAC AGG CTG -3' (FRAG 894) (SEQ. ID NO: 904) 30 T GGC GGG CAC AGG CT-3' (FRAG 895) (SEQ. ID NO: 905) 5'-T GGC GGG CAC AGG C-3' (FRAG 896) (SEQ. ID NO: 906) 5'-T GGC GGG CAC AGG -3' (FRAG 897) (SEO. ID NO: 907) 5'-T GGC GGG CAC AG-3' (FRAG 898) (SEQ. ID NO: 908) 5'-T GGC GGG CAC A-3' (FRAG 899) (SEQ. ID NO: 909) 35 5'-T GGC GGG CAC-3' (FRAG 900) (SEQ. ID NO: 910) 5'-GGC GGG CAC AGG CTG GGC-3' (FRAG 901) (SEQ. ID NO: 911) 5'-GGC GGG CAC AGG CTG GG-3' (FRAG 902) (SEQ. ID NO: 912) 5'-GGC GGG CAC AGG CTG G-3' (FRAG 903) (SEQ. ID NO: 913) 51-GGC GGG CAC AGG CTG -3' (FRAG 904) (SEQ. ID NO: 914) 40 5'-GGC GGG CAC AGG CT-31 (FRAG 905) (SEQ. ID NO: 915) 5'-GGC GGG CAC AGG C-3' (FRAG 906) (SEQ. ID NO: 916) 5'-GGC GGG CAC AGG -3' (FRAG 907) (SEQ. ID NO: 917) 5'-GGC GGG CAC AG-3' (FRAG 908) (SEQ. ID NO: 918) 5'-GGC GGG CAC A-3' (FRAG 909) (SEQ. ID NO: 919) 45 5'-GC GGG CAC AGG CTG GGC-3' (FRAG 910) (SEQ. ID NO: 920) 5'-GC GGG CAC AGG CTG GG-3' (FRAG 911) (SEQ. ID NO: 921) 5'-GC GGG CAC AGG CTG G-3' (FRAG 912) (SEQ. ID NO: 922) GC GGG CAC AGG CTG -3' (FRAG 913) (SEQ. ID NO: 923) 5'- GC GGG CAC AGG CT-3' (FRAG 914) (SEQ. ID NO: 924) 5'- GC GGG CAC AGG C-3' (FRAG 915) (SEQ. ID NO: 925) 5'- GC GGG CAC AGG -3' (FRAG 916) (SEO, ID NO: 926) 5'- GC GGG CAC AG-3' (FRAG 917) (SEO. ID NO: 927) 5'- C GGG CAC AGG CTG GGC-3' (FRAG 918) (SEO. ID NO: 928) 5'- GGG CAC AGG CTG GG-3' (FRAG 919) (SEQ. ID NO: 929) 5'- C GGG CAC AGG C'IG G-3' (FRAG 920) (SEQ. ID NO: 930) 5'- C GGG CAC AGG C'TG -3' (FRAG 921) (SEQ. ID NO: 931) 5'- C GGG CAC AGG CT-3' (FRAG 922) (SEQ. ID NO: 932) 5'- C GGG CAC AGG C-3' (FRAG 923) (SEQ. ID NO: 933) 5'- C GGG CAC AGG -(" (FRAG 924) (SEQ. ID NO: 934) 5'- GGG CAC AGG CTC GGC-3' (FRAG 925) (SEQ. ID NO: 935) 5'- GGG CAC AGG CTC GG-3' (FRAG 926) (SEQ. ID NO: 936)

5'- GGG CAC AGG CTG G-3' (FRAG 927) (SEQ. ID NO: 937)



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5'- GGG CAC AGG CT(3-3' (FRAG 928) (SEQ. ID NO: 938)
5'- GGG CAC AGG CT-3' (FRAG 929) (SEO. ID NO: 939)
5'- GGG CAC AGG C-3' (FRAG 930) (SEQ. ID NO: 940)
5'- GG CAC AGG CTG (GGC-3' (FRAG 931) (SEQ. ID NO: 941)
5'- GG CAC AGG CTG (GG-3' (FRAG 932) (SEQ. ID NO: 942)
5'- GG CAC AGG CTG (3-3' (FRAG 933) (SEQ. ID NO: 943)
5'-GG CAC AGG CTG -3' (FRAG 934) (SEQ. ID NO: 944)
5'- GG CAC AGG CT-3' (FRAG 935) (SEQ. ID NO: 945)
5'-G CAC AGG CTG GC C-3' (FRAG 936) (SEQ. ID NO: 946)
5'-G CAC AGG CTG GC-3' (FRAG 937) (SEQ. ID NO: 947)
5'-G CAC AGG CTG G-3' (FRAG 938) (SEQ. ID NO: 948)
5'-G CAC AGG CTG -3' (FRAG 939) (SEQ. ID NO: 949)
5'-CAC AGG CTG GGC 3' (FRAG 940) (SEQ. ID NO: 950)
5'-CAC AGG CTG GG-3' (FRAG 941) (SEQ. ID NO: 951)
5'-CAC AGG CTG G-3' FRAG 942) (SEQ. ID NO: 952)
5'-AC AGG CTG GGC-3' (FRAG 943) (SEQ. ID NO: 953)
5'-AC AGG CTG GG-3' (FRAG 944) (SEQ. ID NO: 954)
5'-C AGG CTG GGC-3' [FRAG 945] (SEQ. ID NO: 955)
5'-TTT TCC TTC CTT 1GT CTC TCT TC (FRAG 946) (SEQ. ID NO: 956)
5'-GCT CCC GGC TGC CTG (FRAG 947) (SEQ. ID NO: 957)
5'-CTC GGC CGT GCG GCT CTG TCG CTC CCG GT (FRAG 948) (SEQ. ID NO: 958)
5'-CCG CCG CCC TCC 3GG GGG TC (FRAG 949) (SEQ. ID NO: 959)
5'-TGC TGC CGT TGG CTG CCC (FRAG 950) (SEQ. ID NO: 960)
5'-CTT CTG CGG GTC GCC GG (FRAG 951) (SEQ. ID NO: 961)
5'-TGC TGG GCT TGT GGC (FRAG 952) (SEQ. ID NO: 962)
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5'-GGC CTC TCT TCT GGG (FRAG 953) (SEQ. ID NO: 963)
5'-CCT GGT CCC TCC GT (FRAG 954) (SEQ. ID NO: 964)
5'-GGT GGC TCC TCT GC (FRAG 955) (SEQ. ID NO: 965)
5'-GCT TGG TCC TGG GGC TGC (FRAG 956) (SEQ. ID NO: 966)
5'-TGC TCT CCT CTC CTT (FRAG 957) (SEQ. ID NO: 967)

## Human Adenosine A2a Receptor Nucleic Acid and Antisense Oligonucleotide Fragments

5'-CTG GGC CTC-3' (I'RAG 1666) (SEQ. ID NO: 1681)

5'-TGC TTT TCT TTT CTG GGC CTC-3' (FRAG 958) (SEQ. ID NO: 968)

40 5'-TGT GGT CTG TTT TTT TCT G-3' (FRAG 959) (SEQ. ID NO: 969)

5'-GCC CTG CTG GGG CGC TCT CC-3' (FRAG 960) (SEQ. ID NO: 970)

5'-GCC GCC CGC CTG GCT CCC-3' (FRAG 961) (SEQ. ID NO: 971)

5'-GGB GCC CBT GBT GGG CBT GCC-3' (FRAG 962) (SEQ. ID NO: 972)

5'-GTG GTT CTT GCC CTC CTT TGG CTG-3' (FRAG 963) (SEQ. ID NO: 973)

45 5'-CCG TGC CCG CTC CCC GGC-3' (FRAG 964) (SEQ. ID NO: 974)

5'-CTC CTG GCG GGT GGC CGT TG-3' (FRAG 965) (SEQ. ID NO: 975)

5'-GGC CCG TGT TCC CCT GGG-3' (FRAG 966) (SEQ. ID NO: 976)

5'-GCC TGG GGC TCC CTT CTC TC-3' (FRAG 967) (SEQ. ID NO: 977)

5'-GCC CTT CTT GCT (GGG CCT C-3' (FRAG 968) (SEQ. ID NO: 978)

50 5'-TGC TGC TGC TGG TGC TGT GGC CCC C-3' (FRAG 969) (SEQ. ID NO: 979)

5'-GTACACCGAGGAGCCCATGATGGGCATGCCACAGACGACAGGC-3' (FRAG 970) (SEQ. ID NO: 980)

5'-GTBCBCCGBGGGGCCCBTGBTGGGCBTGCCBCBGBCGBCGGC-3' (FRAG 971) (SEQ. ID NO: 981)

## Human Adenosine A2b Receptor Nucleic Acid & Antisense Oligonucleotide Fragments



	GAGGCGCGGT			CGGCGGGTCT	CACGCGGCTG	CCCCTCGCCC	GGCGCGCCTT
	CGGTAGGGG	CGC('CGGGGC	CCAGCTGGCC	CGGCCATGCT	GCTGGAGACA	CAGGACGCGC	TGTACGTGGC
	GCTGGAGCTG	GTCATCGCCG	CGCTTTCGGT	GGCGGCAAC	GTGCTGGTGT	GCGCCGCGGT	GGGCACGGCG
	AACACTCTGC	AGAC'GCCCAC	CAACTACTTC	CTGGTGTCCC	TGGCTGCGGC	CGACGTGGCC	GTGGGGCTCT
5	TCGCCATCCC	CTTTGCCATC	ACCATCAGCC	TGGGCTTCTG	CACTGACTTC	TACGGCTGCC	TCTTCCTCGC
	CTGCTTCGTG	CTGGTGCTCA	CGCAGAGCTC	CATCTTCAGC	CTTCTGGCCG	TGGCAGTCGA	CAGATACCTG
	GCCATCTGTG	TCCCGCTCAG	GTATAAAAGT	TTGGTCACGG	GGACCCGAGC	AAGAGGGGTC	ATTGCTGTCC
	TCTGGGTCCT	TGCCITTGGC	ATCGGATTGA		GGGGTGGAAC		
	CAACTGCACA	GAAC'CCTGGG	ATGGAACCAC			TGAAGTGTCT	CTTTGAGAAT
10	GTGGTCCCCA	TGAC:CTACAT	GGTATATTTC	AATTTCTTTG	GGTGTGTTCT	GCCCCACTG	CTTATAATGC
	TGGTGATCTA	CATTAAGATC	TTCCTGGTGG	CCTGCAGGCA	GCTTCAGCGC	ACTGAGCTGA	TGGACCACTC
	GAGGACCACC		AGATCCATGC		CTGGCCATGA		TTTTGCCCTG
	TGCTGGTTAC	CTGTGCATGC	TGTTAACTGT		TCCAGCCAGC	TCAGGGTAAA	AATAAGCCCA
	AGTGGGCAAT	GAA"ATGGCC	ATTCTTCTGT	CACATGCCAA	TTCAGTTGTC	AATCCCATTG	TCTATGCTTA
15	CCGGAACCGA	GACTTCCGCT	ACACTTTTCA		TCCAGGTATC	TTCTCTGCCA	AGCAGATGTC
	AAGAGTGGGA		TGGGGTACAG		GTGTGGGCCT	ATGATCTAGG	CTCTCGCCTC
		AGATACAAAT		CAAAGAGGAC		TTCATTGTGA	
	CACCTCACAA	GGALATGGAC	TGCCTCTCTT	GAGCACTTCC		CACGTATCTA	GCTAATATGT
	ATGTGTCAGT	AGTAGCACCA					
20	TTATGCCAAC	AGCTTGAATG	GATTCTAACA	GACTCTTTTG	TTTTTAAAAG	AGCTGCTTTT TCTGCCTTGT	ACTGTGTGGA TTATGGTGGA
20	AAATTACTGA	AACTATTTTA	CTGTGAAACA				
		ATA/AAGTTG				AATACTTTTT	AACTTAGAGG
	AAAGTATAAT			CTCACACCTG		GAAGGTGACC	TCAAAAATTA
	GCGGATCACG	AGG''CAGGAG				ACTTTGGGAG	GCCAAGGCAG
25	-	AGACGCGGCA		GCCTGTCCAA		GGGCAATTTG	TTAGTTATCC
2.5	CGAGTGGGTG				CCCCGCGCGG		TGGGCTCGGG
					CGCGGGCCAA		CTCTTGGCCG
		GGCC CTATGG			AGCCCCGAGG		
			CCATGCCCGG	CGGGTCTCAC		CTCGCCCGGC	GCGCCTTCGG
30	TAGGGGGCGC				GGAGACACAG		ACGTGGCGCT
30		ATCGCCGCGC	TTTCGGTGGC			CCGCGGTGGG	CACGGCGAAC
	ACTCTGCAGA	CGCCCACCAA		GTGTCCCTGG	CTGCGGCCGA	CGTGGCCGTG	GGGCTCTTCG
	CCATCCCCTT	TGCCATCACC	ATCAGCCTGG	GCTTCTGCAC	TGACTTCTAC	GGCTGCCTCT	TCCTCGCCTG
	CTTCGTGCTG	GTGCTCACGC	AGAGCTCCAT	CTTCAGCCTT	CTGGCCGTGG	CAGTCGACAG	ATACCTGGCC
25	ATCTGTGTCC	CGCTCAGGTA	TAAAAGTTTG	GTCACGGGGA	CCCGAGCAAG	AGGGGTCATT	GCTGTCCTCT
35	GGGTCCTTGC				GTGGAACAGT		CCACCAACAA
	CTGCACAGAA			TGAAAGCTGC		AGTGTCTCTT	TGAGAATGTG
	GTCCCCATGA	GCTACATGGT	ATATTTCAAT	TTCTTTGGGT	GTGTTCTGCC	CCCACTGCTT	ATAATGCTGG
	TGATCTACAT		CTGGTGGCCT	GCAGGCAGCT	TCAGCGCACT	GAGCTGATGG	ACCACTCGAG
40	GACCACCCTC	CAGCGGGAGA			GCCATGATTG	TGGGGATTTT	TGCCCTGTGC
40	TGGTTACCTG				AGCCAGCTCA		AAGCCCAAGT
	GGGCAATGAA	TATCGCCATT	CTTCTGTCAC	ATGCCAATTC	AGTTGTCAAT	CCCATTGTCT	ATGCTTACCG
					AGGTATCTTC		
					TGGGCCTATG		
4.5					GCTGGTTTTC		
45					GAGCTACCAC		
					ATCTATTCAG		
					TTTAAAAGTC		
					ATAATGCAAA		
					G AGGCTCAGAA		
50					CCCCTCGCCC		
					CAGGACGCGC		
	GTCATCGCCG	CGCTTTCGGT	GGCGGGCAAC	GTGCTGGTGT	GCGCCGCGGT	GGGCACGGCG	AACACTCTGC
					CGACGTGGCC		
					TACGGCTGCC		
55					TGGCAGTCGA		
					AAGAGGGGTC		
	TGCCTTTGGC	ATCGGATTGA	CTCCATTCCT	GGGGTGGAAC	AGTAAAGACA	GTGCCACCAA	CAACTGCACA
	GAACCCTGGG	ATGGAACCAC	GAATGAAAGC	TGCTGCCTTG	TGAAGTGTCT	CTTTGAGAAT	GTGGTCCCCA
	TGAGCTACAT	GGTATATTTC	AATTTCTTTG	GGTGTGTTCT	GCCCCACTG	CTTATAATGC	TGGTGATCTA



	CATTAAGATC			GCTTCAGCGC		TGGACCACTC	GAGGACCACC
	CTCCAGCGGG	AGAT'CCATGC		CTGGCCATGA	TTGTGGGGAT	TTTTGCCCTG	TGCTGGTTAC
	CTGTGCATGC	TGTTAACTGT	GTCACTCTTT	TCCAGCCAGC	TCAGGGTAAA	AATAAGCCCA	AGTGGGCAAT
_	GAATATGGCC	ATTC TTCTGT	CACATGCCAA	TTCAGTTGTC	AATCCCATTG	TCTATGCTTA	CCGGAACCGA
5	GACTTCCGCT	ACACTTTTCA	CAAAATTATC	TCCAGGTATC	TTCTCTGCCA	AGCAGATGTC	AAGAGTGGGA
	ATGGTCAGGC	TGGCGTACAG	CCTGCTCTCG	GTGTGGGCCT	ATGATCTAGG	CTCTCGCCTC	TTCCAGGAGA
	AGATACAAAT	CCAC AAGAAA	CAAAGAGGAC	ACGGCTGGTT	TTCATTGTGA	AAGATAGCTA	CACCTCACAA
	GGAAATGGAC	TGCCTCTCTT	GAGCACTTCC	CTGGAGCTAC	CACGTATCTA	GCTAATATGT	ATGTGTCAGT
	AGTAGCACCA	AGGATTGACA	AATATATTTA	TGATCTATTC	AGCTGCTTTT	ACTGTGTGGA	TTATGCCAAC
10	AGCTTGAATG	GAT1 CTAACA	GACTCTTTTG	TTTTTAAAAG	TCTGCCTTGT	TTATGGTGGA	AAATTACTGA
	AACTATTTTA	CTGT GAAACA	GTGTGAACTA	TTATAATGCA	AATACTTTTT	AACTTAGAGG	CAATGGAAAA
	ATAAAAGTTG	ACTGTACTAA	AAATGTATAC	TTGTTGCCAG	GAAGGTGACC	TCAAAAATTA	AAAGTATAAT
	TATTCGGCCG	GGCATGGTGG	CTCACACCTG	TAATTCCAGC	ACTTTGGGAG	GCCAAGGCAG	GCGGATCACG
	AGGTCAGGAG	TTCAAAACCA	GCCTGTCCA	A TATAGTG	GGGCAATTTG	TTAGTTATCC	GCCGCCACCA
15	AGACGCGGCA	CGGCGCCTGG	ACCGGAGGGG			TGGGCTCGGG	CGAGTGGGTG
	GTGCTCCGCC	CAGCCCGAGA	CGGGCGGGCG	CGCGGGCCAA	TGGGTGCCGC	CTCTTGGCCG	CGGGGGGCCC
	CGACCCGTGG	GTCCCGGCCA	CCAGCGCCCC	AGCCCCGAGG		GCAGGCGGAG	GCGCGGTCCG
	GGCGCTATGG	CCATGCCCGG	CGGGTCTCAC	GCGGCTGCCC	CTCGCCCGGC	GCGCCTTCGG	TAGGGGGCGC
	CCGGGGCCCA	GCTGGCCCGG	CCATGCTGCT	GGAGACACAG	GACGCGCTGT	ACGTGGCGCT	GGAGCTGGTC
20	ATCGCCGCGC	TTTCGGTGGC	GGGCAACGTG	CTGGTGTGCG	CCGCGGTGGG	CACGGCGAAC	ACTCTGCAGA
	CGCCCACCAA	CTACTTCCTG	GTGTCCCTGG	CTGCGGCCGA	CGTGGCCGTG	GGGCTCTTCG	CCATCCCCTT
	TGCCATCACC	ATCAGCCTGG	GCTTCTGCAC	TGACTTCTAC	GGCTGCCTCT	TCCTCGCCTG	CTTCGTGCTG
	GTGCTCACGC	AGAC CTCCAT	CTTCAGCCTT	CTGGCCGTGG	CAGTCGACAG	ATACCTGGCC	ATCTGTGTCC
	CGCTCAGGTA	TAAAAGTTTG	GTCACGGGGA	CCCGAGCAAG	AGGGGTCATT	GCTGTCCTCT	GGGTCCTTGC
25	CTTTGGCATC	GGATTGACTC	CATTCCTGGG	GTGGAACAGT		CCACCAACAA	CTGCACAGAA
	CCCTGGGATG	GAAC CACGAA	TGAAAGCTGC	TGCCTTGTGA	AGTGTCTCTT	TGAGAATGTG	GTCCCCATGA
	GCTACATGGT	ATATTTCAAT	TTCTTTGGGT	GTGTTCTGCC	CCCACTGCTT	ATAATGCTGG	TGATCTACAT
	TAAGATCTTC	CTGG'TGGCCT	GCAGGCAGCT	TCAGCGCACT	GAGCTGATGG	ACCACTCGAG	GACCACCCTC
	CAGCGGGAGA	TCC#TGCAGC	CAAGTCACTG	GCCATGATTG	TGGGGATTTT	TGCCCTGTGC	TGGTTACCTG
30	TGCATGCTGT	TAACIGTGTC	ACTCTTTTCC	AGCCAGCTCA	GGGTAAAAAT	AAGCCCAAGT	GGGCAATGAA
	TATGGCCATT	CTTC'IGTCAC	ATGCCAATTC	AGTTGTCAAT	CCCATTGTCT	ATGCTTACCG	GAACCGAGAC
	TTCCGCTACA	CTTT 'CACAA	AATTATCTCC	AGGTATCTTC	TCTGCCAAGC	AGATGTCAAG	AGTGGGAATG
	GTCAGGCTGG	GGTACAGCCT	GCTCTCGGTG	TGGGCCTATG	ATCTAGGCTC	TCGCCTCTTC	CAGGAGAAGA
	TACAAATCCA	CAAGAAACAA	AGAGGACACG	GCTGGTTTTC	ATTGTGAAAG	ATAGCTACAC	CTCACAAGGA
35	AATGGACTGC	CTCTCTTGAG	CACTTCCCTG	GAGCTACCAC	GTATCTAGCT	AATATGTATG	TGTCAGTAGT
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				O: 1670) (SEQ. ID			
40	5'- GGGCAATT	TG TTAGTTATC	C GCCGCCACC	A AGACGCGGCA	A CGGCGCCTGG	ACCGGAGGGG	CCCCGCGCGG
	GCGCGAACTT				CAGCCCGAGA		
					GTCCCGGCCA		
					CCATGCCCGG		
					GCTGGCCCGG		
45					TTTCGGTGGC		
					CTACTTCCTG		CTGCGGCCGA
		GGGCTCTTCG			ATCAGCCTGG		TGACTTCTAC
	GGCTGCCTCT		CTTCGTGCTG		AGAGCTCCAT		
<b>50</b>					TAAAAGTTTG		CCCGAGCAAG
50					GGATTGACTC		
					GAACCACGAA		
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					CTGGTGGCCT		TCAGCGCACT
~~					TCCATGCAGC		GCCATGATTG
55	TGGGGATTTT	TGCCCTGTGC		TGCATGCTGT		ACTCTTTTCC	AGCCAGCTCA
					CTTCTGTCAC		AGTTGTCAAT
	CCCATTGTCT	ATGC'ITACCG	GAACCGAGAC		CTTTTCACAA		AGGTATCTTC
					GGTACAGCCT		TGGGCCTATG
	ATCTAGGCTC	TCGCCTCTTC	CAGGAGAAGA	TACAAATCCA	CAAGAAACAA	AGAGGACACG	GCTGGTTTTC



ATTGTGAAAG ATAGCTACAC CTCACAAGGA AATGGACTGC CTCTCTTGAG CACTTCCCTG GAGCTACCAC GTATCTAGCT AATATGTATG TGTCAGTAGT AGGCTCCAAG GATTGACAAA TATATTTATG ATCTATTCAG CTGCTTTTAC TGTGIGGATT ATGCCAACAG CTTGAATGGA TTCTAACAGA CTCTTTTGTT TTTAAAAGTC TGCCTTGTTT ATGGIGGAAA ATTACTGAAA CTATTTTACT GTGAAACAGT GTGAACTATT ATAATGCAAA TACTTTTTAA CTTAG.AGGCA ATGGAAAAAT AAAAGTTGAC TGTACTAAAA ATG-3'(FRAG.NO: )(SEQ.ID NO:2436) 5'-CCCAGCCCCG AGGCTCAGAA GCGGCAGGCG GAGGCGCGGT CCGGGCGCTA TGGCCATGCC CGGCGGGTCT CACGCGGCTG CCCCTCGCCC GGCGCGCCTT CGGTAGGGGG CGCCCGGGGC CCAGCTGGCC CGGCCATGCT GCTGGAGACA CAGGACGCGC TGTACGTGGC GCTGGAGCTG GTCATCGCCG CGCTTTCGGT GGCGGGCAAC GTGCTGGTGT GCGCCGCGGT GGGCACGGCG AACACTCTGC AGACGCCCAC CAACTACTTC CTGGTGTCCC TGGCTGCGGC CGACGTGGCC GTGGGGCTCT TCGCCATCC CTTTGCCATC ACCATCAGCC TGGGCTTCTG CACTGACTTC TACGGCTGCC TCTTCCTCGC CTGCTTCGTG CTGGTGCTCA CGCAGAGCTC CATCTTCAGC CTTCTGGCCG TGGCAGTCGA CAGATACCTG GCCATCTGTG TCCCGCTCAG GTATAAAAGT TTGGTCACGG GGACCCGAGC AAGAGGGGTC ATTGCTGTCC TCTGGGTCCT TGCCTTTGGC ATCGGATTGA CTCCATTCCT GGGGTGGAAC AGTAAAGACA GTGCCACCAA CAACTGCACA GAACCCTGGG ATGGAACCAC GAATGAAAGC TGCTGCCTTG TGAAGTGTCT CTTTGAGAAT GTGGTCCCCA TGAGCTACAT GGTATATTTC AATTTCTTTG GGTGTGTTCT GCCCCCACTG CTTATAATGC TGGTGATCTA CATTAAGATC TTCCTGGTGG CCTGCAGGCA GCTTCAGCGC ACTGAGCTGA TGGACCACTC GAGGACCACC CTCCAGCGGG AGATCCATGC AGCCAAGTCA CTGGCCATGA TTGIGGGGAT TTTTGCCCTG TGCTGGTTAC CTGTGCATGC TGTTAACTGT GTCACTCTTT TCCAGCCAGC TCAGGGTAAA AATAAGCCCA AGTGGGCAAT GAATATGGCC ATTCTTCTGT CACATGCCAA TTCAGTTGTC AATCCCATTG TCTATGCTTA CCGGAACCGA GACTTCCGCT ACACTTTTCA CAAAATTATC TCCAGGTATC TTCT/TGCCA AGCAGATGTC AAGAGTGGGA ATGGTCAGGC TGGGGTACAG CCTGCTCTCG GTGTGGGCCT ATGATCTAGG CTCTCGCCTC TTCCAGGAGA AGATACAAAT CCACAAGAAA CAAAGAGGAC ACGGCTGGTT TTCATTGTGA AAGATAGCTA CACCTCACAA GGAAATGGAC TGCCTCTCTT GAGCACTTCC CTGGAGCTAC CACCTATCTA GCTAATATGT ATGTGTCAGT AGTAGCACCA AGGATTGACA AATATATTTA TGATCTATTC AGCTGCTTTT ACTGTGGGA TTATGCCAAC AGCTTGAATG GATTCTAACA GACTCTTTTG TTTTTAAAAG TCTGCCTTGT TTATGGTGGA AAATTACTGA AACTATTTTA CTGTGAAACA GTGTGAACTA TTATAATGCA AATACTTTTT AACTTAGAGG CAATGGAAAA ATAAAAGTTG ACTGTACTAA AAATGTATAC TTGTTGCCAG GAAGGTGACC TCAAAAATTA AAAGTATAAT TATTCGGCCG GGCATGGTGG CTCACACCTG TAATTCCAGC ACTTIGGGAG GCCAAGGCAG GCGGATCACG AGGTCAGGAG TTCAAAACCA GCCTGTCCAA TATAGTG -3' (FRAG. NO: ) (SEO. ID NO:2435) 5'- GGGCAATTTG TTAGTTATCC GCCGCCACCA AGACGCGGCA CGGCGCCTGG ACCGGAGGGG CCCCGCGCGG GCGCGAACTT TGGGCTCGGG CGAGTGGGTG GTGCTCCGCC CAGCCCGAGA CGGGCGGGCG CGCGGGCCAA TGGGTGCCGC CTCTTGGCCG CGGGGGGCCC CGACCCGTGG GTCCCGGCCA CCAGCGCCCC AGCCCCGAGG CTCAGAAGCG GCACGCGGAG GCGCGGTCCG GGCGCTATGG CCATGCCCGG CGGGTCTCAC GCGGCTGCCC CTCGCCCGGC GCGCCTTCGG TAGGGGGCGC CCGGGGCCCA GCTGGCCCGG CCATGCTGCT GGAGACACAG GACGCGCTGT ACGTGGCGCT GGAGCTGGTC ATCGCCGCGC TTTCGGTGGC GGGCAACGTG CTGGTGTGCG CCGCGGTGGG CACCGCGAAC ACTCTGCAGA CGCCCACCAA CTACTTCCTG GTGTCCCTGG CTGCGGCCGA CGTGGCCGTG GGGCTCTTCG CCATCCCCTT TGCCATCACC ATCAGCCTGG GCTTCTGCAC TGACTTCTAC GGCTGCCTCT TCCTCGCCTG CTTCGTGCTG GTGCTCACGC AGAGCTCCAT CTTCAGCCTT CTGGCCGTGG CAGTCGACAG ATACCTGGCC ATCTGTGTCC CGCTCAGGTA TAAAAGTTTG GTCACGGGGA CCCGAGCAAG AGGGGTCATT GCTCTCCTCT GGGTCCTTGC CTTTGGCATC GGATTGACTC CATTCCTGGG GTGGAACAGT AAAGACAGTG CCACCAACAA CTGCACAGAA CCCTGGGATG GAACCACGAA TGAAAGCTGC TGCCTTGTGA AGTGTCTCTT TGAGAATGTG GTCCCCATGA GCTACATGGT ATATTTCAAT TTCTTTGGGT GTGTTCTGCC CCCACTGCTT ATAATGCTGG TGATCTACAT TAAGATCTTC CTGGTGGCCT GCAGGCAGCT TCAGCGCACT GAGCTGATGG ACCACTCGAG GACCACCCTC CAGCGGGAGA TCCATGCAGC CAAGTCACTG GCCATGATTG TGGGGATTTT TGCCCTGTGC TGGTTACCTG TGCATGCTGT TAACTGTGTC ACTCTTTTCC AGCCAGCTCA GGGTAAAAAT AAGCCCAAGT GGGCAATGAA TATGGCCATT CTTCTGTCAC ATGCCAATTC AGTTGTCAAT CCCATTGTCT ATGCITACCG GAACCGAGAC TTCCGCTACA CTTTTCACAA AATTATCTCC AGGTATCTTC TCTGCCAAGC AGATGTCAAG AGTGGGAATG GTCAGGCTGG GGTACAGCCT GCTCTCGGTG TGGGCCTATG ATCTAGGCTC TCGCCTCTTC CAGGAGAAGA TACAAATCCA CAAGAAACAA AGAGGACACG GCTGGTTTTC ATTGTGAAAG ATACCTACAC CTCACAAGGA AATGGACTGC CTCTCTTGAG CACTTCCCTG GAGCTACCAC GTATCTAGCT AATATGTATG TGTCAGTAGT AGGCTCCAAG GATTGACAAA TATATTTATG ATCTATTCAG CTGCTTTTAC TGTGTGGATT ATGCCAACAG CTTGAATGGA TTCTAACAGA CTCTTTTGTT TTTAAAAGTC TGCCTTGTTT ATGGTGGAAA ATTACTGAAA CTATTTTACT GTGAAACAGT GTGAACTATT ATAATGCAAA TACTTTTTAA CTTAGAGGCA ATGGAAAAAT AAAAGTTGAC TGTACTAAAA ATG-3'(FRAG. NO: )(SEQ.ID NO:2425) 5'-CCCAGCCCCG AGGCTCAGAA GCGGCAGGCG GAGGCGCGGT CCGGGCGCTA TGGCCATGCC CGGCGGGTCT CACGCGGCTG CCCCTCGCCC GGCGCGCCTT CGGTAGGGGG CGCCCGGGGC CCAGCTGGCC CGGCCATGCT GCTGGAGACA CAGGACGCC TGTACGTGGC GCTGGAGCTG GTCATCGCCG CGCTTTCGGT GGCGGGCAAC GTGCTGGTGT GCGCCGCGGT GGGCACGGCG AACACTCTGC AGACGCCCAC CAACTACTTC CTGGTGTCCC



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TATAGTG (FRAG. NO ) ( SEQ. ID NO: 2424)
5'-GCGCGTCCTG-3' FRAG. NO: 1671) (SEQ. ID NO:1686)
5'-GCT GGG CCC CGG 3' (FRAG. NO: 1672) (SEQ. ID NO:1687)
5'-CGG GTC GGG GCC CCC C-3' (FRAG. NO: 1673) (SEQ. ID NO:1688)
5'- CGC GCC CGC G-3' (FRAG. NO: 1674) (SEO. ID NO:1689)
5'-GGC GCC GTG CCG CGT CTT GGT GGC GGC GG-3' (FRAG 972) (SEO. ID NO: 982)
5'-GTT CGC GCC CGC GCG GGG CCC CTC CGG TCC-3' (FRAG 973) (SEQ. ID NO: 983)
5'-GTT CGC GCC CGC GCG GGG CCC CTC CGG TCC-3' (FRAG 974) (SEQ. ID NO: 984)
5'-CGG GTC GGG GCC CCC CGC GGC C-3' (FRAG 975) (SEQ. ID NO: 985)
5'-GCC TCG GGG CTG GGG CGC TGG TGG CCG GG-3' (FRAG 976) (SEQ. ID NO: 986)
5'-CCG CGC CTC CGC CTG CCG CTT CTG-3' (FRAG 977) (SEO. ID NO: 987)
5'-GCT GGG CCC CGG GCG CCC CCT-3' (FRAG 978) (SEQ. ID NO: 988)
5'-CCC CTC TTG CTC (GGG TCC CCG TG-3' (FRAG 979) (SEQ. ID NO: 989)
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## Human Adenosine A3 Receptor Nucleic Acid and Antisense Oligonucleotide Fragments

5'-ACAGCGCGTCCTGTGTCTCCAGCAGCATGGCCGGGCCAGCTGGGCCCC-3' (FRAG 980) (SEQ. ID NO: 990) 5'-BCBGCGCGTCCTGTGTCTCCBGCBGCBTGGCCGGGCCBGCTGGGCCCC-3' (FRAG 981) (SEQ. ID NO: 991)

5'-ACA GAG CAG TGC TGT TGT TGG GCA TCT TGC CTT CCC AGG G BCB GBG CB TGC TGT TGT TGG GCB TCT GAATTCCCAG ATGGCCAGAG GTGGCTGGCC TGGTGACCCT AAGTGTGTCT CCTGCCTTTA TTCTCTCTAG TGGGTTATTC TTTCATGTGG TATCTTGCCT ACAGCATGCT GTGTTTGGAC ACAAACCCCT TTCCTTGGTT TCTC GACCC AGCTGAGATG GACTGATTCC AAAAGAACTC ACCTATGTAC TGGGGTAGGG GAGGGAGGGT TTT1TGCAGT ATTTAACTAA GGTTCAAAGA GTGCTATATA GTGAGAAAGG CTTCTTTTTT TTTTTTTTT TTTTTTGGCA GAGTGCTGCC TCCTAGAAAT TTCTCTTGGT AACTTCCTTC TCTGAAGCAC AGATAAAGAA AACAATTACA GTAGAAACAT TTATGAGGGA CACATTGGAG GCCGATGAAG CTTTTCAAGT TCCAGCAGTG CAGGGATGTG GGCAGAACTG ACATTGGAAA ATACTAGAAT GATGGAAATT CAGTTGGAGA GGACTGCCCT TTTT.AATGTC TGGGGAGTCT GCTCAGGGAG AAATGACAAG TCTGGCGGGG ACAAGTATGG GATTTGGTAA GACTTGGATC AACTTGGGAT ACAGGGTGGG GGTCGGGAGT GGAATCAATG AATGATGCCA GAGCAGATCA ACTAACAAGA GGACCCTGAT GAGCCCCAGG CAGAGGCGTC TCCCTTATGC CCCACTCTGA AGTGTTTGTT AGTAAACACC AGAACGCCAT TGTTGTTACT GCTGAATTTT ATTTTGGGCT GTACATATTT AGATGCTTAA GGTAAAAATG ATAAAGCCCT CAAGCCACTG TGTGGGTTTG GGTCCAAGTG TTCCTTCTTG CTGCCTCTCT AACACGCCTG GTTAAAATAA TCCCTTTGGA TGGTGCTGAG AAGCACCTGA ACCAAGTGGG TCCCCAAATA ACAATGGCGT GCAAGTGTCT GGTTCCCAGA AGTTGGTGAC TAGGTAAGCA GCTTCAGGGA GAGGGGGCTG ATTCCCAGAC AGTCGCCTGT TCCTGCGGGG ATGGGGCTGA GGCTTGGGGA ATGTGGGCAG GAGGATATGC CAT TGATTC TGTTGCACAC GTTCTTTTCC CTTCTTTCTG TATGTCTGGT CATTCTGCTA TTCTGTCGTT CCTC.\CATAG GTTGGACATT GGCCGGCTGC CAGCATAAGT GCCAGTGTGA TTTTGCTAGG TGTGAGCTGA GAAAGAGG TGGAGGCTAA GCAGGTGTGA TGCTTCTCAG AGGTGCTGAG TTTTTGCCCT TCTGAGCAGG GAATCTTTGC TTATCCCTTT GACCAAGGAT CTTTGCTGCA AAGGCTGGGT ATCGGCTGTG





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	GGGCTGAACA	TGTCTGTGGT			TTGTGGAATT		CCTGCTCTCG
					GAGTTTAAGG C		
	GAATTCCCAG	ATGGGCAGAG				CCTGCCTTTA	TTCTCTCTAG
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• •		GGCA.GAACTG	ACATTGGAAA		GATGGAAATT	CAGTTGGAGA	GGACTGCCCT
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					GCCCTTTCTA		



ATCACCCCAC CAGAAAAGGG TAGGAATGAG CAAGTTGGGA ATTTTAGACT GTCACTGCAC ATGGACCTCT GGGAAGACGT CTGCCCGAGAG CTAGGCCCAC TGGCCCTACA GACGGATCTT GCTGGCTCAC CTGTCCCTGT GGAGGTTCCC CTGGGAAGGC AAGATGCCCA ACAACAGCAC TGCTCTGTCA TTGGCCAATG TTACCTACAT CACCATGGAA ATTITCATTG GACTCTGCGC CATAGTGGGC AACGTGCTGG TCATCTGCGT GGTCAAGCTG AACCCCAGCC TGCAGACCAC CACCTTCTAT TTCATTGTCT CTCTAGCCCT GGCTGACATT GCTGTTGGGG TGCTGGTCAT GCCTTTGCC ATTGTTGTCA GCCTGGGCAT CACAATCCAC TTCTACAGCT GCCTTTTTAT GACTTGCCTA CTGCTTATCT TTACCCACGC CTCCATCATG TCCTTGCTGG CCATCGCTGT GGACCGATAC TTGCGGGTCA AGCTTACCGT CAGATACAAG AGGGTCACCA CTCACAGAAG AATATGGCTG GCCCTGGGCC TTTGCTGGCT GGTGTCATTC CTGGTGGGAT TGACCCCCAT GTTTGGCTGG AACATGAAAC TGACCTCAGA GTACCACAGA AATCTCACCT TCCTTTCATG CCAATTTGTT TCCGTCATGA GGATGGACTA CATGGTATAC TTCAGCTTCC TCACCTGGAT TTTCATCCCC CTGGTTGTCA TGTGCGCCAT CTATCTTGAC ATCTTTTACA TCATTCGGAA CAAACTCAGT CTGAACTTAT CTAACTCCAA AGAGACAGGT GCATTTTATG GACGGGAGTT CAAGACGGCT AAGTCCTTGT TTCTGGTTCT TTTCTTGTTT GCTCTGTCAT GGCTGCCTTT ATCTCTCATC AACTGCATCA TCTACTTTAA TGGTGAGGTA CCACAGCTTG TGCTGTACAT GGGCATCCTG CTGTCCCATG CCAACTCCAT GATGAACCCT ATCGTCTATG CCTATAAAAT AAAGAAGTTC AAGGAAACCT ACCTTTTGAT CCTCAAAGCC TGTGTGGTCT GCCATCCCTC TGATTCTTTG GACACAAGCA TTGAGAAGAA TTCTGAGTAG TTATCCATCA GAGATGACTC TGTCTCATTG ACCTTCAGAT TCCCCATCAA CAAACACTTG AGGGCCTGTA TGCCTGGGCC AAGCGATTTT TACATCCTTG ATTACTTCCA CTGAGGTGGG AGCATCTCCA GTGCTCCCCA ATTATATCTC CCCCACTCCA CTACTCTCTT CCTCCACTTC ATTTTTCCTT TGTCCTTTCT CTCTAATTCA GTGTTTTGGA GGCCTGACTT GGGGACAACG TATTATTGAT ATTATTGTCT GTTTTCCTTC TTCCCAATAG AAGAATAAGT CATCGAGCCT GAAGGGTGCC TAGTTGACTT ACTGACAAAA GGCTCTAGTT GGGCTGAACA TGTGTGTGT GGTGACTCAT TTCCATGCCA TTGTGGAATT GAGCAGAGAA CCTGCTCTCG GAGGATGCCT AGGAGATGTT GGGAACAGAA GAAATAAACT GAGTTTAAGG GGGACTTAAA CTGCTGAATT C -3' (FRAG. NO:1675) (SEQ. ID NO:3007) 5'- CGAATTCGGG GCACATCTGT TTGGGGAACT AAGAGCAGCA GCACTTTCAG ATTCAGTCCA TATAGAGCTG TCCTACAGCA TTCT/GGAAAC TTGAGGATGT GCGGTGCATA AACGGGCTGG AAGTGACCCA CCTGTGATGA GCCCTTTCTA AGGAGAAGGG TTTCCAAGAG ATCACCCCAC CAGAAAAGGG TAGGAATGAG CAAGTTGGGA ATTITAGACT GTCACTGCAC ATGGACCTCT GGGAAGACGT CTGGCGAGAG CTAGGCCCAC TGGCCCTACA GACGGATCTT GCTGGCTCAC CTGTCCCTGT GGAGGTTCCC CTGGGAAGGC AAGATGCCCA ACAACAGCAC TGCTCTGTCA TTGGCCAATG TTACCTACAT CACCATGGAA ATTTTCATTG GACTCTGCGC CATAGTGGGC AACGTGCTGG TCATCTGCGT GGTCAAGCTG AACCCCAGCC TGCAGACCAC CACCTTCTAT TTCATTGTCT CTCTAGCCCT GGCTGACATT GCTGTTGGGG TGCTGGTCAT GCCTTTGGCC ATTGTTGTCA GCCTGGGCAT CACAATCCAC TTCTACAGCT GCCTTTTTAT GACTTGCCTA CTGCTTATCT TTACCCACGC CTCCATCATG TCCTTGCTGG CCATGCTGT GGACCGATAC TTGCGGGTCA AGCTTACCGT CAGATACAAG AGGGTCACCA CTCACAGAAG AATATGGCTG GCCCTGGGCC TTTGCTGGCT GGTGTCATTC CTGGTGGGAT TGACCCCCAT GTTTGGCTGG AACATGAAAC TGACCTCAGA GTACCACAGA AATGTCACCT TCCTTTCATG CCAATTTGTT TCCGTCATGA GGATGGACTA CATGGTATAC TTCAGCTTCC TCACCTGGAT TTTCATCCCC CTGGTTGTCA TGTGCGCCAT CTATCTTGAC ATCTTTTACA TCATTCGGAA CAAACTCAGT CTGAACTTAT CTAACTCCAA AGAGACAGGT GCA'TTTATG GACGGGAGTT CAAGACGGCT AAGTCCTTGT TTCTGGTTCT TTTCTTGTTT GCTCTGTCAT GGCTGCCTTT ATCTCTCATC AACTGCATCA TCTACTTTAA TGGTGAGGTA CCACAGCTTG TGCTGTACAT GGGCATCCTG CTGTCCCATG CCAACTCCAT GATGAACCCT ATCGTCTATG CCTATAAAAT AAAGAAGTTC AAGGAAACCT ACCTTTTGAT CCTCAAAGCC TGTGTGGTCT GCCATCCCTC TGATTCTTTG GACACAAGCA TTGAGAAGAA TTCTGAGTAG TTATCCATCA GAGATGACTC TGTCTCATTG ACCTTCAGAT TCCCCATCAA CAAACACTTG AGGGCCTGTA TGCCTGGGCC AAGGGATTTT TACATCCTTG ATTACTTCCA CTGAGGTGGG AGCATCTCCA GTGCTCCCCA ATTATATCTC CCCCACTCCA CTACTCTCTT CCTCCACTTC ATTTTCCTT TGTCCTTTCT CTCTAATTCA GTGTTTTGGA GGCCTGACTT GGGGACAACG TATTATTGAT ATTATTGTCT GTTT CCTTC TTCCCAATAG AAGAATAAGT CATGGAGCCT GAAGGGTGCC TAGTTGACTT ACTGACAAAA GGCTCTAGTT GGGCTGAACA TGTGTGTGGT GGTGACTCAT TTCCATGCCA TTGTGGAATT GAGCAGAGAA CCTCCTCTG GAGGATGCCT AGGAGATGTT GGGAACAGAA GAAATAAACT GAGTTTAAGG GGGACTTAAA CTGCTGAATT C -3' (FRAG. NO: ) (SEQ. ID NO:2439) 5'- CTGCTGAATT TTATTTTGGA CTGTACATAT TTAGATGCTT AAGGTAAAAA TGATAAAGCC CTCAAGCCAC TGTGTGGGTT GGGTCCAAGT GTTCCTTGCT GCTGCCTCTC TAACACGCCT GGTTAAAATA ATCCCTTTGG ATGGTGCTGA GAAGCACCTG AACCAAGTGG GTCCCCAAAT AACTATGGCG TGCAAGTGTC TGGTTCCCAG AAGTTGGTGA CTAGGTAAGC GACTCAGGGA GAGGGGCTGA TTCCCAGACA GTCGCCTGTT CCTGCTGGGA TGGGGCTGAG GCTTGGGGAA TGTGGGCAGG AGGATATGCC ATTTGATTCT GTTGCACACG TTCTTTTCCC TTCTTTCTGT ATGTCTGGTC ATTCTGCTAT TCTGTCGTTC CTCACATAGG TTGGACATTG GCCGGCTGCC AGCATAAGTG CCAGTGTGAT TTTGCTAGGG TGTGAGCTGA GAAAGAGGG TGGAGGCTAA GCAGGTGTGA TGCTTCTCAG AGGTGCTGAG TTTTTGCCCT TCTGAGCAGG GAATCTTTGC TTATCCCTTT GACCAAGGAT CTTTGCTCCA AAGGCTGGGT ATCGGCTGTG CTCAGCAAAG CGTCAACTCG TGCAAGAACT TAGCAGGAAT



			GGCTGCCACC			CTGCTTCTCC	CGTTTGCCTC
	CTTATCATGA	GATCTTTTTG	CTAAGCTGGC			GCTTCCAGCT	CCGCTCCCAC
	CTGATCCTGC	ACTGTCCTCT	GGTCCCTGAA	TGAATGAACT	CTGATACCCA	ATCTTGTCTC	GAGCCTTCTC
	TATGCCACTC	ATGC CTCCTC	TTCTGCTCTT	TCCATCTTTT	TGCTGAGAGT	TACTGAGCTC	TGTACTTCCT
5	CTTGGCCCAT	CTCACTTCCT	GAAACACCCC	TGAAGAGGGT	TGCTTATCTT	GATGGAACTC	AAAAAGCCAA
	AAAGCTGCAG	GCAGAGGCGT	TGAGGACATC	TGTTTGGGGA	ACTAAGAGCA	GCAGCACTTT	CAGATTCAGT
	CCATATAGAG	CTGTCCTACA	GCATTCTGGA	AACTTGAGGA	TGTGCGGTGC	ATAAAGGGGC	TGGAAGTGAC
	CCACCTGTGA	TGAGCCCTTT	CTAAGGAGAA	GGGTTTCCAA	GAGATCACCC	CACCAGAAAA	GGGTAGGAAT
	GAGCAAGTTG	GGAATTTTAG	ACTGTCACTG	CACATGGACC	TCTGGGAAGA	CGTCTGGCGA	GAGCTAGGCC
10	CACTGGCCCT	ACAGACGGAT	CTTGCTGGCT	CACCTGTCCC	TGTGGAGGTT	CCCCTGGGAA	GGCAAGATGC
	CCAACAACAG	CACTCCTCTG -3	' (FRAG. NO:_) (	SEQ. ID NO:2438)	1		
	5'- GAATTCCC	AG ATGGGCAG	AG GTGGCTGG	GC TGGTGACCC	T AAGTGTGTC	T CCTGCCTTTA	TTCTCTCTAG
	TGGGTTATTC	TTTC ATGTGG	TATCTTGCCT	ACAGCATGCT	GTGTTTGGAC	ACAAACCCCT	TTCCTTGGTT
	TCTCTGACCC	AGCT GAGATG	GACTGATTCC	AAAAGAACTC	ACCTATGTAC	TGGGGTAGGG	GAGGGAGGGT
15	TTTTTGCAGT	ATTT AACTAA	GGTTCAAAGA	GTGCTATATA	GTGAGAAAGG	CTTCTTTTT	TTTTTTTTT
	TTTTTTGGCA	GAGTGCTGCC	TCCTAGAAAT	TTCTCTTGGT	AACTTCCTTC	TCTGAAGCAC	AGATAAAGAA
	AACAATTACA	GTAC AAACAT	TTATGAGGGA	CACATTGGAG	GCCGATGAAG	CTTTTCAAGT	TCCAGCAGTG
			ACATTGGAAA				
	TTTTAATGTC		GCTCAGGGAG				
20			ACAGGGTGGG				
		GGACCCTGAT			TCCCTTATGC		AGTGTTTGTT
	AGTAAACACC			GCTGAATTTT	ATTTTGGGCT	GTACATATTT	AGATGCTTAA
		ATAMAGCCCT	CAAGCCACTG		GGTCCAAGTG		CTGCCTCTCT
		GTTAAAATAA			AAGCACCTGA		TCCCCAAATA
25			GGTTCCCAGA			GCTTCAGGGA	
23			TCCTGCGGGG				
	CATTTGATTC	TGTTGCACAC	GTTCTTTTCC	CTTCTTTCTG	TATGTCTGGT	CATTCTGCTA	TTCTGTCGTT
			GGCCGGCTGC			TTTTGCTAGG	TGTGAGCTGA
			GCAGGTGTGA			TTTTTGCTAGG	TCTGAGCAGG
30	GAATCTTTGC		GACCAAGGAT	CTTTGCTGCA		ATCGGCTGTG	CTCAGCAAAG
50		TGCAAGAACT			AAGGTTAGGA		AAAGTCTCTT
	TTTTGTTCCT	CTGCTTCTCC			GATCTTTTTG	CTAAGCTGGC	AGAAAGATTG
	CATAGTCAGT	GCTTCCAGCT	CTGCTCCCAC		ACTGTCCTCT	GGTCCCTGAA	TGAATGAACT
	CTGATACCCA	ATC1TGTCTC	GAGCCTTCTC	TATGCCACTC	ATGGCTCCTC	TTCTGCTCTT	TCCATCTTTT
35	TGCTGAGAGT	TCTC AGCTCT	GTACTTCCTC	TTGGCCCATC		AAACACCCCT	GAAGAGGGTT
33			AAAAGCCAAA			GAGGACATCT	GTTTGGGGAA
		CAGCACTTTC		CATATAGAGC		CATTCTGGAA	
	GTGCGGTGCA	TAA# GGGGCT ACC#GAAAAG					
40					GAATTTTAGA		ACATGGACCT
40			AGCTAGGCCC		CAGACGGATC		
			GCAAGATGCC				
			TGGACTCTGC				
			ACCACCTTCT				
15			CCATTGTTGT				
45			CTTTACCCAC				
			GTCAGGTAGC			CAATTGAGGC	AGCTGGGAAA
			3' (FRAG. NO:_) (	_			
			T TTGGGGAACT				
50			TTGAGGATGT				
50			TTTCCAAGAG				
			ATGGACCTCT				
			CTGTCCCTGT				
			TTACCTACAT				
			GGTCAAGCTG				
55			GCTGTTGGGG				
			GCCTTTTTAT				
			GGACCGATAC				
			GCCCTGGGCC				
	GTTTGGCTGG	AACA.TGAAAC	TGACCTCAGA	GTACCACAGA	AATGTCACCT	TCCTTTCATG	CCAATTTGTT

40



TCCGTCATGA GGAIGGACTA CATGGTATAC TTCAGCTTCC TCACCTGGAT TTTCATCCCC CTGGTTGTCA TGTGCGCCAT CTATCTTGAC ATCTTTTACA TCATTCGGAA CAAACTCAGT CTGAACTTAT CTAACTCCAA AGAGACAGGT GCA'TTTATG GACGGGAGTT CAAGACGGCT AAGTCCTTGT TTCTGGTTCT TTTCTTGTTT GCTCTGTCAT GGCTGCCTTT ATCTCTCATC AACTGCATCA TCTACTTTAA TGGTGAGGTA CCACAGCTTG TGCTGTACAT GGGCATCCTG CTGTCCCATG CCAACTCCAT GATGAACCCT ATCGTCTATG CCTATAAAAT AAAGAAGTTC AAGGAAACCT ACCTTTTGAT CCTCAAAGCC TGTGTGGTCT GCCATCCCTC TGATTCTTTG GACACAAGCA TTG&GAAGAA TTCTGAGTAG TTATCCATCA GAGATGACTC TGTCTCATTG ACCTTCAGAT TCCCCATCAA CAAACACTTG AGGGCCTGTA TGCCTGGGCC AAGGGATTTT TACATCCTTG ATTACTTCCA CTGAGGTGGG AGCATCTCCA GTGCTCCCCA ATTATATCTC CCCCACTCCA CTACTCTCTT CCTCCACTTC ATTITICCTT TGTC/TTTCT CTCTAATTCA GTGTTTTGGA GGCCTGACTT GGGGACAACG TATTATTGAT ATTATTGTCT GTTT CCTTC TTCCCAATAG AAGAATAAGT CATGGAGCCT GAAGGGTGCC TAGTTGACTT ACTGACAAAA GGCTCTAGTT GGGCTGAACA TGTGTGTGGT GGTGACTCAT TTCCATGCCA TTGTGGAATT GAGCAGAGAA CCTCCTCCG GAGGATGCCT AGGAGATGTT GGGAACAGAA GAAATAAACT GAGTTTAAGG GGGACTTAAA CTGCTGAATT C -3' (FRAG. NO:\_) (SEQ. ID NO:2427) 5'-TTCCCAG ATGGGCAGAG GTGGCTGGGC TGGTGACCCT AAGTGTGTCT CCTGCCTTTA TTCTCTCTAG TGGGTTATTC TTTCATGTGG TATCTTGCCT ACAGCATGCT GTGTTTGGAC ACAAACCCCT TTCCTTGGTT TCTCTGACCC AGCT3AGATG GACTGATTCC AAAAGAACTC ACCTATGTAC TGGGGTAGGG GAGGGAGGGT TTTTTGCAGT ATTTAACTAA GGTTCAAAGA GTGCTATATA GTGAGAAAGG CTTCTTTTTT TTTTTTTTT TTTTTTGGCA GAGTGCTGCC TCCTAGAAAT TTCTCTTGGT AACTTCCTTC TCTGAAGCAC AGATAAAGAA AACAATTACA GTACAAACAT TTATGAGGGA CACATTGGAG GCCGATGAAG CTTTTCAAGT TCCAGCAGTG CAGGGATGTG GGCAGAACTG ACATTGGAAA ATACTAGAAT GATGGAAATT CAGTTGGAGA GGACTGCCCT TTTTAATGTC TGGGGAGTCT GCTCAGGGAG AAATGACAAG TCTGGCGGGG ACAAGTATGG GATTTGGTAA GACTTGGATC AACTTGGGAT ACAGGGTGGG GGTCGGGAGT GGAATCAATG AATGATGCCA GAGCAGATCA ACTAACAAGA GGACCCTGAT GAGCCCCAGG CAGAGGCGTC TCCCTTATGC CCCACTCTGA AGTGTTTGTT AGTAAACACC AGAACGCCAT TGTTGTTACT GCTGAATTTT ATTTTGGGCT GTACATATTT AGATGCTTAA GGTAAAAATG ATAAAGCCCT CAAGCCACTG TGTGGGTTTTG GGTCCAAGTG TTCCTTCTTG CTGCCTCTCT AACACGCCTG GTTAAAATAA TCCCTTTGGA TGGTGCTGAG AAGCACCTGA ACCAAGTGGG TCCCCAAATA ACAATGGCGT GCAAGTGTCT GGTTCCCAGA AGTTGGTGAC TAGGTAAGCA GCTTCAGGGA GAGGGGGCTG ATTCCCAGAC AGTCGCCTGT TCCTGCGGGG ATGGGGCTGA GGCTTGGGGA ATGTGGGCAG GAGGATATGC CATTTGATTC TGTTGCACAC GTTCTTTTCC CTTCTTTCTG TATGTCTGGT CATTCTGCTA TTCTGTCGTT CCTCACATAG GTTGGACATT GGCCGGCTGC CAGCATAAGT GCCAGTGTGA TTTTGCTAGG TGTGAGCTGA GAAAGAGAGG TGGAGGCTAA GCAGGTGTGA TGCTTCTCAG AGGTGCTGAG TTTTTGCCCT TCTGAGCAGG GAATCTTTGC TTATCCTTT GACCAAGGAT CTTTGCTGCA AAGGCTGGGT ATCGGCTGTG CTCAGCAAAG CGTCAACTCG TGCAAGAACT TAGCAGGAAT AGTTCTGGCT AAGGTTAGGA GGCTGCCACC AAAGTCTCTT TTTTGTTCCT CTGCTCTCC CGTTTGCCTC CTTATCATGA GATCTTTTTG CTAAGCTGGC AGAAAGATTG CATAGTCAGT GCTTCCAGCT CTGCTCCCAC CTGATCCTGC ACTGTCCTCT GGTCCCTGAA TGAATGAACT CTGATACCCA ATCITGTCTC GAGCCTTCTC TATGCCACTC ATGGCTCCTC TTCTGCTCTT TCCATCTTTT TGCTGAGAGT TCTGAGCTCT GTACTTCCTC TTGGCCCATC TCACTTCCTG AAACACCCCT GAAGAGGGTT GCTTATCTTG ATGGAACTCA AAAAGCCAAA AAGCTGCAGG CAGAGGCGTT GAGGACATCT GTTTGGGGAA CTAAGAGCAG CAGCACTTTC AGATTCAGTC CATATAGAGC TGTCCTACAG CATTCTGGAA ACTTGAGGAT GTGCGGTGCA TAAAGGGGCT GGAAGTGACC CACCTGTGAT GAGCCCTTTC TAAGGAGAAG GGTTTCCAAG AGATCACCCC ACCAGAAAAG GGTAGGAATG AGCAAGTTGG GAATTTTAGA CTGTCACTGC ACATGGACCT CTGGGAAGAC GTCTGGCGAG GCTAGGCCC ACTGGCCCTA CAGACGGATC TTGCTGGCTC ACCTGTCCCT GTGGAGGTTC CCTCGGAAG GCAAGATGCC CAACAACAGC ACTGCTCTGT CATTGGCCAA TGTTACCTAC TCACCATGG AAATTTCAT TGGACTCTGC GCCATAGTGG GCAACGTGCT GGTCATCTGC GTGGTCAAGC TGAACCCCAG CCTGCAGACC ACCACCTTCT ATTTCATTGT CTCTCTAGCC TGGCTGACA TTGCTGTTGG
GGTGCTGGTC ATGCCTTTGG CCATTGTTGT CAGCCTGGGC TCACAATCC ACTTCTACAG CTGCCTTTTT
ATGACTTGCC TACTGCTTAT CTTTACCCAC CCTCCATCA TGTCCTTGCT GGCCATCGCT GTGGACCGAT ACTTGCGGGT CAAGCTTACC GTCAGGTAGC CTGCGGCGTG GGGTGGGCAG CAATTGAGGC AGCTGGGAAA TGAGGCTACA AGCCAGAGC-3' (FRAG. NO: ) (SEQ. ID NO:2426) 5'-GGGCAATTTG TT/-GTTATCC GCCGCCACCA AGACGCGGCA CGGCGCCTGG ACCGGAGGGG CCCCGCGCGG GCGCGAACTT TGGGCTCGGG CGAGTGGGTG GTGCTCCGCC CAGCCCGAGA CGGGCGGGCG CGCGGGCCAA TGGGTGCCGC CTCTTGGCCG CGGGGGGCCC CGACCCGTGG GTCCCGGCCA CCAGCGCCCC AGCCCCGAGG CTCAGAAGCG GCAGGGGGG GCGCGGTCCG GGCGCTATGG CCATGCCCGG CGGGTCTCAC GCGGCTGCCC CTCGCCCGGC GCGCCTTCGG TAGGGGGCGC CCGGGGCCCA GCTGGCCCGG CCATGCTGCT GGAGACACAG GACGCGCTGT ACGTGGCGCT GGAGCTGGTC ATCGCCGCGC TTTCGGTGGC GGGCAACGTG CTGGTGTGCG CCGCGGTGGG CACGGCGAAC ACTCTGCAGA CGCCCACCAA CTACTTCCTG GTGTCCCTGG CTGCGGCCGA CGTGGCCGTG GGGCTCTTCG CCATCCCCTT TGCCATCACC ATCAGCCTGG GCTTCTGCAC TGACTTCTAC GGCTGCCTCT TCCTCGCCTG CTTCGTGCTG GTGCTCACGC AGAGCTCCAT CTTCAGCCTT CTGGCCGTGG



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CAGTCGACAG ATACCTGGCC ATCTGTGTCC CGCTCAGGTA TAAAAGTTTG GTCACGGGGA CCCGAGCAAG
    AGGGGTCATT GCTCTCTCT GGGTCCTTGC CTTTGGCATC GGATTGACTC CATTCCTGGG GTGGAACAGT
    AAAGACAGTG CCAC'CAACAA CTGCACAGAA CCCTGGGATG GAACCACGAA TGAAAGCTGC TGCCTTGTGA
    AGTGTCTCTT TGAGAATGTG GTCCCCATGA GCTACATGGT ATATTTCAAT TTCTTTGGGT GTGTTCTGCC
    CCCACTGCTT ATAATGCTGG TGATCTACAT TAAGATCTTC
                                                   CTGGTGGCCT GCAGGCAGCT TCAGCGCACT
    GAGCTGATGG ACCACTCGAG GACCACCCTC CAGCGGGAGA TCCATGCAGC CAAGTCACTG GCCATGATTG
    TGGGGATTTT TGCCCTGTGC TGGTTACCTG TGCATGCTGT TAACTGTGTC ACTCTTTTCC AGCCAGCTCA
    GGGTAAAAAT AAGCCCAAGT GGGCAATGAA TATGGCCATT CTTCTGTCAC ATGCCAATTC AGTTGTCAAT
    CCCATTGTCT ATGCTTACCG GAACCGAGAC TTCCGCTACA CTTTTCACAA AATTATCTCC AGGTATCTTC
    TCTGCCAAGC AGATGTCAAG AGTGGGAATG GTCAGGCTGG GGTACAGCCT GCTCTCGGTG TGGGCCTATG
    ATCTAGGCTC TCGCCTCTTC CAGGAGAAGA TACAAATCCA CAAGAAACAA AGAGGACACG GCTGGTTTTC
    ATTGTGAAAG ATACCTACAC CTCACAAGGA AATGGACTGC CTCTCTTGAG CACTTCCCTG GAGCTACCAC
    GTATCTAGCT AATATGTATG TGTCAGTAGT AGGCTCCAAG GATTGACAAA TATATTTATG ATCTATTCAG
    CTGCTTTTAC TGTGTGGATT ATGCCAACAG CTTGAATGGA TTCTAACAGA CTCTTTTGTT TTTAAAAGTC
15
    TGCCTTGTTT ATGGTGGAAA ATTACTGAAA CTATTTTACT GTGAAACAGT GTGAACTATT ATAATGCAAA
    TACTTTTTAA CTTAGAGGCA ATGGAAAAAT AAAAGTTGAC TGTACTAAAA ATG-3'(FRAG. NO: )(SEQ.ID NO:2425)
    5'-GBG CB TGC-3' (FRAG. NO:1676) (SEO. ID NO:1691)
    5'-TTG TTG GGC-3' (J'RAG. NO:1677) (SEQ. ID NO:1692)
    5'-TGC CTT CCC BGG 3-3' (FRAG. NO:1678) (SEO. ID NO:1693)
    5'-GTT GTT GGG CAT CTT GCC-3' (FRAG. NO:1679) (SEQ ID NO:3)
    5'-GTG GGC CTA GCT CTC GCC-3' (GRAG. NO:1680) (SEQ ID NO:5)
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- - 5'-ACA GAG CA TGC TGT TGT TGG GCA TCT TGC CTT CCC AGG G-3' (FRAG 982) (SEO. ID NO: 992) 5'-BCB GBG CB TGC TIJT TGT TGG GCB TCT TGC CTT CCC BGG G-3' (FRAG 983) (SEQ. ID NO: 993)
  - 5'-CCC TTT TCT GGT (GGG GTG-3' (FRAG 984) (SEQ. ID NO: 994)
- 5'-GTG CTG TTG TTG 3GC-3' (FRAG 985) (SEO. ID NO: 995)
  - 5'-TTT CTT CTG TTC ('C-3' (FRAG 986) (SEO. ID NO: 996) 5'-CCC TTT TCT GGT (3GG GTG-3' (FRAG 987) (SEQ. ID NO: 997)
  - 5'-GTG CTG TTG TTG 3GC-3' (FRAG 988) (SEQ. ID NO: 998)
  - 5'-TTT CTT CTG TTC ('C-3' (FRAG 989) (SEQ. ID NO: 999)

# Human IgE Recept or β Nucleic Acid and Antisense Oligonucleotide Fragments

TTC ATT AAC CGA GOT GT BTT TGC TCT CCT BTT BCT TTC TGT GTC CBT TTT TTC BTT BBC CGB GCT GT-3' (FRAG. NO:1681) (SE(). ID NO:1694)

- 5'-CCC CTG GG-3' (FRAG. NO:1682) (SEQ. ID NO:1695)
- 5'-GCTCTCCTBTT-3' (I'RAG. NO:1683) (SEQ. ID NO:1696)
  - 5'-CBTTBBCCGBGCTG-3' (FRAG. NO:1684) (SEQ. ID NO:1697)
  - 5'-TTT CCC CTG GGT CTT CC-3' (FRAG 990) (SEQ. ID NO: 1000)
  - 5'-CTC CTG CTC TTT 1'TT C-3' (FRAG 991) (SEQ. ID NO: 1001)
  - ATTTGCTCTCTATTACTTTCTGTGTCCATTTTTTCATTAACCGAGCTGT (FRAG 992) (SEQ. ID NO: 1002)
- 40 BTTTGCTCTCTBTTBCTTTCTGTGTCCBTTTTTTCBTTBBCCGBGCTGT (FRAG 993) (SEO. ID NO: 1003)

#### Human Fc-E Receptor CD23 Antigen (IgE Receptor) Nucleic Acid and Antisense Oligonucleotide Fragments

- C GGG TCT TGC TCT GGG CCT GGC TGT GGC CGT GGT TGG GGG TCT TC GCT GCC TCC GTT TGG GTG GC TCT CTG AAT ATT GAC CIT CCT CCA TGG CGG TCC TGC TTG GAT TCT CCC GA TCT CTG BBT BTT GBC CTT CCT CCB TGG CGG TCC TC C TTG GBT TCT CCC GB-3'(FRAG 1685)(SEO.ID NO:1698)
  - 5'-GT CCT CCT-3' (FRAG 1686) (SEQ. ID NO: 1699)
  - 5'-TGT GTC TGT CCT CC-3' (FRAG 1687) (SEQ. ID NO: 1700)
- 5'-GTG GCC CTG GC-3' (FRAG 1688) (SEQ. ID NO: 1701)
  - 5'-CGT GGT TGG GG-3' (FRAG 1689) (SEQ. ID NO: 1702)
  - 5'-TCT CTG BBT BTT (GBC C-3' (FRAG1690) (SEQ. ID NO:1703)
  - 5'-GCC TGT GTC TGT CCT CCT-3' (FRAG 994) (SEQ. ID NO: 1004)
  - 5'-GCT TCG TTC CTC ''CG TTC-3' (FRAG 995) (SEQ. ID NO:1005)
- 5'-CTG CTT GGT GCC CTT GCC G-3' (FRAG 996) (SEQ. ID NO: 1006)
  - 5'-GTC CTG CTC CTG GCT GTG G-3' (FRAG 997) (SEQ. ID NO: 1007)
  - 5'-GTC GTG GCC CTG GCT CGG GCT GGT GGG CTC CCC TGG-3' (FRAG 998) (SEQ. ID NO: 1008)
  - 5'-CCT TCG CTG GCT (GGC GGC GTG C-3' (FRAG 999) (SEQ. ID NO: 1009)



5'-GGG TCT TGC TCT (GGG CCT GGC TGT-3' (FRAG 1000) (SEO. ID NO: 1010)

5'-GGC CGT GGT TGG GGG TCT TC-3' (FRAG 1001) (SEQ. ID NO: 1011)

5'-GCT GCC TCC GTT FGG GTG GC (FRAG 1002) (SEQ. ID NO: 1012)

5'-TCT CTG AAT ATT 'JAC CTT CCT CCA TGG CGG TCC TGC TTG GAT TCT CCC GA (FRAG 1003) (SEQ.ID NO:1013)

5'-TCT CTG BBT BTT (iBC CTT CCT CCB TGG CGG TCC TGC TTG GBT TCT CCC GB (FRAG 1004) (SEQ.ID NO:1014)

## Human IgE Recept or α Subunit Nucleic Acid and Antisense Oligonucleotide Fragments

5'- GCC TTT CCT GGT TCT CTT GTT GTT TTT GGG GTT TGG CTT ACA GTA GAG TAG GGG ATT CCA TGG CAG GAG CCA TCT TCT TC'A TGG ACT CC TTC AAG GAG ACC TTA GGT TTC TGA GGG ACT GCT AAC ACG CCA TCT GGA GC BCB GTB GEG TBG GGG BTT CCB TGG CBG GBG CCB TCT TCT TCB TGG BCT CC TTC BBG GBG BCC TTB GGT TTC TGB GC G BCT GCT BBC BCG CCB TCT GGB GC GTT GTT TTT GGG GTT TGG CTT GCC TTT CCT GGT TCT CTT BCB GTB GBG TBG GGG BTT CCB TGG CBG GBG CCB TCT TCT TCB TGG BCT CC TTC BBG GBG BCC TTB GGT TTC TGB GGG BCT GCT BBC BCG CCB TCT GGB GC-3' (FRAG. NO: 1691) (SEQ. ID NO:1704)
5'- TGG BCT CC -3' (FRAG. NO: 1692) (SEQ. ID NO:1705)

5'-CCB TCT GGB-3' (I'RAG. NO: 1693) (SEQ. ID NO:1706)

- 15 5'-CT GCT BBC BCG-3' (FRAG. NO: 1694) (SEQ. ID NO:1707)
  - 5'-GTT TTT GGG GTT 'TG-3' (FRAG. NO: 1695) (SEQ. ID NO:1708)
  - 5'-GCC TTT CCT GGT 'I'CT CTT GTT GTT TTT GGG GTT TGG CTT-3' (FRAG. NO:1005) (SEQ. ID NO:1015)
  - 5'-ACAGTAGAGTAGGGGAGTCCATGGCAGGAGCCATCTTCTTCATGGACTCC-3'(FRAG.NO:1006)(SEQ.ID NO:1016)
  - 5'-TTC AAG GAG ACC TTA GGT TTC TGA GGG ACT GCT AAC ACG CCA TCT GGA GC-3' (FRAG. NO:1007) (SEQ.
- 20 ID NO:1017)
  - 5'-BCB GTB GBG TBG '3GG BTT CCB TGG CBG GBG CCB TCT TCT TCB TGG BCT CC TTC BBG GBG BCC TTB GGT TTC TGB GGG-3' (FRAG. NO:1008) (SEQ. ID NO:1018)
  - 5'-BCT GCT BBC BCG CCB TCT GGB GC-3' (FRAG. NO:1009) (SEQ. ID NO:1019)
  - 5'-GTT GTT TTT GGG GTT TGG CTT-3' (FRAG. NO:1010) (SEQ. ID NO:1020)
- 25 5'-GCC TTT CCT GGT 'CT CTT-3' (FRAG. NO:1011) (SEQ. ID NO:1021)
  - 5'-BCBGTBGBGTBGGGGBTTCCBTGGCBGGBGCCBTCTTCTTCBTGGBCTCC-3'(FRAG.NO:1012) (SEQ.ID NO:1022)
    5'-TTC BBG GBG BCC TTB GGT TTC TGB GGG BCT GCT BBC BCG CCB TCT GGB GC-3' (FRAG.NO:1013) (SEQ.ID NO:1023)

#### Human IgE Recept or (Fc Epsilon R) Nucleic Acid and Antisense Oligonucleotide Fragments

- 35 5'-TCG TTC CTC TCG-3' (FRAG: 1697) (SEQ. ID NO:3001)
  - 5'-BGB BCG BGB C-3' (FRAG: 1698) (SEQ. ID NO:1711)
  - 5'-TGB BTB TTGB-3' (FRAG: 1699) (SEQ. ID NO:1712)
  - 5'-GCC TGT GTC TGT CCT CCT-3' (FRAG. NO:1014) (SEQ. ID NO:1024)
  - 5'-GCT TCG TTC CTC TCG TTC-3' (FRAG. NO:1015)(SEQ. ID NO:1025)
- 40 5'-CTG CTT GGT GCC CTT GCC G-3' (FRAG. NO:1016)(SEQ. ID NO:1026)
  - 5'-GTC CTG CTC CTG GGG GCT GTG G-3' (FRAG. NO:1017)(SEQ. ID NO:1027)
  - 5'-GTC CTC GCC CTG GCT CCG GCT GGT GGG CTC CCC TGG-3' (FRAG. NO:1018) (SEQ. ID NO:1028)
  - 5'-CCT TCG CTG GCT '3GC GGC GTG C-3' (FRAG. NO:1019) (SEQ. ID NO:1029)
  - 5'-CCC BGB BCG BGB CCC GGB CCG BCB-3' (FRAG. NO:1020) (SEQ. ID NO:1030)
- 45 5'-GGC CGT GGT TGG GGG TCT TC-3' (FRAG. NO:1021) (SEQ. ID NO:1031)
  - 5'-GCT GCC TCC GTT 'IGG GTG GC-3' (FRAG. NO:1022) (SEQ. ID NO:1032)
  - 5'-GBT CTC TGB BTB "TGB CCT TCC BTG GCG GTC CTG CTT GGB-3" (FRAG. NO:1023) (SEQ. ID NO:1033)

#### Human High Affinity IgE Receptor Oligonucleotide Fragments

5'-AACAAGAAAA GCGTTGGTAG CTCTGGTGAA TCCCAAAAGA ATGTGGCAGT TGCTAGCCAT GCTCCTGAAT

ATGTATAAAC AGTACATCAT ATGACTAAGA GTTTGACTTA GGGGTTAGAT TTTATGTGTT TGAACCCCAA
ATTAGTTATT TAATAGTTGG CACCCCAAAA CAAGTTACTT AACCTCACTA AGGTTCAGTT TTCCTGTTTA
TAAAATGTAG ATACTGATAG TATGTACTTT ATAGGATAAT TGTGAAAAAT AAATGAAATA TCAGATTTAT
TTAGGATAAC ACCTGGCATA TGTTTGGTAT TCAGAATTAG TTGCTGCTGT TTTATTCTGC TCTCCCTTGC
ATCCCACTTT TCTAAGTTGT AAACTAAATA GTTGTACACA GATTGACAGA TTAAGAAAGG CTTGTGATTG

55 TGCTAGACCT ATGCCTATGC CTCTGTCTCA CCAGATTCCA GGTGTATATG TGGAGGTGGG ATAGGGAGTG
GAGTAAGTGG GTAAATATA AATTGCCCAG TTGGGCACCA TCCTGAATAT TATCTCTAAA GAAAGAAGCA
AAACCAGGCA CAGCTGATGG GTTAACCAGA TATGATACAG AAAACATTTC CTTCTGCTTT TTGGTTTTAA
GCCTATATTT GAAGCCTTAG ATCTCTCCAG CACAGTAAGC ACCAGGAGTC CATGAAGAAG ATG
TGGAATGACT GGTTTCATC AATAGACTTA ATTCAGCAGT CTGTGGGGAA GAGCAAGGTA

60 GTTCCTCAAG TGCTTCAGAT GTGAAGTGGG TTTAAATATA CTGTCCCTGT CTTCTTCAGA GTTTTGGTAA



	ACATA A A ATA	CCACACTCAT	TT	TOTTO A A A	TCACAACCCA	CTATACACAT	TA ATTA CA COTT
				TCTTTGCAAA			
				TCCTGGAAGA			
				GCCCCTGCTG			
_				GCTAGGAAGT			
5	CCATAAGTAA			TGTGTTCTGA			
	GTCTCTGAAA	ATGTTTCCAA	TTTCGCTGGT			AATCAGATGA	
	ATTTATGCAC	TAACIGATCA		AAACAAGAAA			
	AATTTGGCAG	TTGCTAGCCA		TATGTATAAA		TATGACTAAG	AGTTTGACTT
	AGGGGTTAGA	TTTTATGTGT	TTGAACCCCA	AATTAGTTAT	TTAATAGTTG	GCACCCCAAA	ACAAGTTACT
10	TAACCTCACT	AAGA TTCAGT	TTTCCTGTTT	ATAAAATGTA		GTATGTACTT	TATAGGATTA
	TTGTGAAAAA	TAAA.TGAAAT	ATCAGATTTA	TTTAGGATAA	CACCTGGCAT	ATGTTTGGTA	TTCAGTAATT
	AGTTGCTGCT	GTTT TATTCT		GCATCCCACT	TTTCTAAGTT	GTAAACTAAA	TAGTTGTACA
	CAGATTGACA	GATI AAGAAA	GGCTTGTGAT	TGTGCTAGAC	CTATGCCTCT	CTCTCACCAG	ATTCCAGGTG
	TATATGTGGA	GGTGGGATAG	GGAGTGGAGT	AAGTGGGTAA	ATATTAAATT	GCCCAGTTGG	GCACCATCCT
15	GAATATTATC	TCTA.\AGAAA	GAAGCAAAAC	CAGGCACAGC	TGATGGGTTA	ACCAGATATG	ATACAGAAAA
	CATTTCCTTC	TGCTTTTTGG	TTTTAAGCCT	ATATTTGAAG	CCTTAGATCT	CTCCAGCACA	GTAAGCACCA
	GGAGTCCATG	AAGAAGATGG	CTCCTGCCAT	GGAATCCCCT	ACTCTACTGT	GTGTAGCCTT	ACTGTTCTTC
	GGTAAGTAGA	<b>GATT CAATTA</b>	CCCCTCCCAG	GGAGGCCCAA	ATGAATTTGG	GGAGCAGCTG	GGGTAGGAAC
	CTTTACTGTG	GGTGGTGACT	TTTTCTAGGA	CATGTGCAAA	CTATTGGGCA	TTTCCCAGGG	ACTCTGTAGT
20	GGAGCCAAGC	TAGAAAGCAG	AGGCAAGTGG	GCTGAGCAAC	ACCTAAGGAG	GAAGCCAGAC	TGAAAGCTTG
	GTTCCTTGCA	TTTGCTCTGG			TCCTACCAAG		TAGAGGAGAG
	AAAGAAGCTC	TTTCTTCCCC	TGATTCTCAT	TCCTGAAAAG	ACGGTTGGTC	CTTAAAATTC	CATGGATGTA
	GATCTTATCC	CCACACCCAG	ATTCTAGTCC	TCTGGAGATA	AAGAAGACTG	CTGGACACTA	
	TCTGGACTTT	TGCAGCTCCA	GATGGCGTGT	TAGCAGGTGA		CTTGTTCCCT	TGGTGTATCA
25	ACATGTCTGG	GCATTGCTTT	CCTCTCACTA	TTTTCTTCGT	CCCATCACTT	CTGCTTTCTA	ATGAGCATGA
	ATCTGTTCCT	TGGCCAGACT	ACTTTCCCTC	TCCACCTTGC	CTTGTCTTTC	TTTTTTTCCC	TGATTCATTG
	CATTCTCTCA	AGTCATTCTC	TCCTCTGTTT	TAGTCAATAA	CCATGTCTGT	TGCACATATA	CATGTCTCAT
	TCTCTCTCCT	AGACACTTTG	GCATGATCTC	GCTCAATAAT	TACATTATTA	TTATTATTGC	CATTTTATAA
	TTGAGGATGC	TGAAACTCAG		GTGGTTACAT			
30	CTTGGATCTA	AGTC CAGTTC	TCTTCTGACT	ATATCACCCT	TTTGTTATCA	CCATGTATCT	ACTTCTTTGG
20	TCTCTGTTCA	AATTIGCACT	ACATCCCCTT	GTTCCAGGAA	GCCATTCAAG	ACTGACTTTC	TTAGTGCCTC
	TCACTACTTT	CTGGAACTGA	CATATGTTTT	TCACTCTGTA	TATACTTACA	ATTAAATAGT	CATAAATATT
	CAGAGCTTGG	AGAAACCTTA		AGTCCAGTAA		CCATAATTCA	CTCATTCATT
	CACATAATAA	ATATTTAATG	TAACAATGGT	TGAACATGGC	AGACAGTGTT	TCTACCTCAA	
35	AGTCCTCATT	TACAGATACT	GAATTGAAAT	TAACAGAAGT	AGAGTGAGTC	AGCTCAAATC	ACATAGTGAA
22	TTGGTTTCTT	TGTTTTTAAA	TCTCCTGCAT	ATGTGTCCTG	TCTTTCTCCC	TGTGTTGGGC	GTTCCCTGGG
						ACCAACAGAA	
	TTGACCACTG	ATTCTCAGAA	TATTGCTTCG	TTTGTACTTT	TAAGCCTAGA	CAGTTTTCAA	TGACTTTTTT
	TCTCTCTACA	TGTCITTTCA	TATTTTTATC		CCCTCAGAAA	CCTAAGGTCT	CCTTGAACCC
40	TCCATGGAAT		AAGGAGAGAA		ACATGTAATG		CTTTGAAGTC
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				GTCAGCACCA			
				TGGAAATACA			
				TAGGACACCA			
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				CACCTGTAGT			
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				AATAAATAAA			
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				GGATCAAAAG			
				CTCTTCGTTA			
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				TCCCTGACTT			
	CATTAAATAA	AGAATTACAT	AAGTAATTAA	TTTAAATTAT	ACATGITTIG	AAGAAGTTTT	TTTTTGACAA



	CYT A TO A A TYT A A	CA CT: A CA A CT	GGG L LOTTEG	m.m. 1.00m. 1	a.a.aa.a.		ama am
		CACTAGAACT			GAGAGGACAA		CTCCTAAGCT
		AGAAAGACTG	TTTATTTTCC			AACAGAAGAT	CTGAAAGGAA
	TTCTGGCTTT	CAACTGTTCC	ATGTATGGAC	TCATCAGGGA	GGTCCGAGAG	GCTTTGTGGC	CCCAGACTGA
5	CTTTTCAGGA	GGGGAAAGGA	TTTATCAATA				CCCTTTAAAA
5	ATCCACTTTA	TGACCCAAAA	AGTGAGTTAA		TAGTTTCTGA	CACATGCTCT	ATGCGTGGCT
	CTCTTTTCTC CTGGCTGCTC	TATTCATTCT	CTCTCTCTTC	ATTTATTGTT	AAATAAATAA	TGTAATGAAT	GTTCTTCAGA
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	GCCTGTGAAG	TAT CACTTT	TGAAGGAGAA		TTCCTTCACA	CACTTTGTAC	ATAATAATGT
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	TGAGAATCAC	TTGTCTAGGT	GATCTTTAAA	TGATTTCTGG	ATGTAATATT	CTGAGGCTCT	ATAATTTGAG
25	ACTAATCACA	AAA/\TCGGTA	CAGTTTATAA	ACAGACTAAC	AGAACCACAA	AATAATAGAA	TTGGAAGGCA
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	ACATAGAAAC	GTC GTGCTC	AAGGATTTAT	AGAAATGCTT	CATTAAACTG	AGTGAAACTG	GTTAAGTGGC
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					GGAGTCCATG		CTCCTGCCAT
					GCTCCAGATG		
<b>~</b> 0					TTAAAGGAGA		
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					GGAGAATACA		
					GGCTGCTCCT		
					GAGGAACTGG		
<b>.</b> .					CACAACATCT		
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					ATTTTTTATC		
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00					ATGCTTCATT		
					ATAAATGAGA		
	INCOMITICI	DIADAUAAAA	TICAATITCA	AIAAAAIAAA	TATAAAACCA	IGIAACAGAA	1GC11C1GAG





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	TNTGTAAATG	TTTGGTAAAA	ATATCATCAT	GTACNTTTTC	ATAATTACGC	TATNTNCACA	TGATATATGT
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	TTCATGCTCC	ATCC AGGACC	TAATGAATAA	GAATCTGCAT	TTTAGCAAGA	CCCTCATATG	ATTCATATAC
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	CTATATCCAC	ATCC ACAGTT	GCCAGAAATT	TTTTGAGACC	AAGTGCTTTA	TGGCTTCCTT	TTCCACTGTA
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						GGCCAAAGCT	
						TGTACTAAAA	
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5'-GATCTTCATG TGGAATGACT GGTTTCATTC AATAGACTTA ATTCAGCAGT CTGTGGGGAA GAGCAAGGTA TGATAGAATG GTTCCTCAAG TGCTTCAGAT GTGAAGTGGG TTTAAATATA CTGTCCCTGT CTTCTTCAGA GTTTTGGTAA AGATAAAATA GGACACTCAT TTAAAAGCAA TCTTTGCAAA TGACAAGCCA CTATAGACAT TAATAGAGTT TTC/.TTTCCA GTATTATCAT TAATATCAGA TCCTGGAAGA AGGTTGAGCC TTGACCTAGA GCAAAAAAAC AGAAGAATTA GTAAAGGAAT CCTGGAGAAA GCCCCTGCTG TGTATTTAAA GGAGAAAGGG GCCTAGATCC CCATAAGTAA TGGTTTAACT TCTGCCTTCC TGTGTTCTGA GCCAGATTAG GGCACAGTAG AGAAAGAGGA GTCICTGAAA ATGTTTCCAA TTTCGCTGGT CAGACAGCGG ATCATCAGTG AATCAGATGA AAATTTGTGG ATTTATGCAC TAACTGATCA GCAGGAAATT AAACAAGAAA AGCGTTGGTA GCTCTGGTGA ATCCCAAAAG AAT TGGCAG TTGCTAGCCA TGCTCCTGAA TATGTATAAA CAGTACATCA TATGACTAAG AGTTTGACTT AGGGGTTAGA TTTTATGTGT TTGAACCCCA AATTAGTTAT TTAATAGTTG GCACCCCAAA ACAAGTTACT TAACCTCACT AAGATTCAGT TTTCCTGTTT ATAAAATGTA GATAGTGATA GTATGTACTT 15 TATAGGATTA TTG1GAAAAA TAAATGAAAT ATCAGATTTA TTTAGGATAA CACCTGGCAT ATGTTTGGTA TTCAGTAATT AGTTGCTGCT GTTTTATTCT GCTCTCCCTT GCATCCCACT TTTCTAAGTT GTAAACTAAA TAGTTGTACA CAGATTGACA GATTAAGAAA GGCTTGTGAT TGTGCTAGAC CTATGCCTCT CTCTCACCAG GCACCATCCT GAATATTATC TCTAAAGAAA GAAGCAAAAC CAGGCACAGC TGATGGGTTA ACCAGATATG ATACAGAAAA CATITCCTTC TGCTTTTTGG TTTTAAGCCT ATATTTGAAG CCTTAGATCT CTCCAGCACA GTAAGCACCA GGAGTCCATG AAGAAGATGG CTCCTGCCAT GGAATCCCCT ACTCTACTGT GTGTAGCCTT ACTGTTCTTC GGTAAGTAGA GATTCAATTA CCCCTCCCAG GGAGGCCCAA ATGAATTTGG GGAGCAGCTG GGGTAGGAAC CTT'ACTGTG GGTGGTGACT TTTTCTAGGA CATGTGCAAA CTATTGGGCA TTTCCCAGGG ACTCTGTAGT GGACCCAAGC TAGAAAGCAG AGGCAAGTGG GCTGAGCAAC ACCTAAGGAG GAAGCCAGAC TGAAAGCTTG GTTC:CTTGCA TTTGCTCTGG CATCTTCCAG AGTGCAAATT TCCTACCAAG GTAATGAGGG TAGAGGAGAG AAAGAAGCTC TTTCTTCCCC TGATTCTCAT TCCTGAAAAG ACGGTTGGTC CTTAAAATTC CATGGATGTA GATCTTATCC CCACACCCAG ATTCTAGTCC TCTGGAGATA AAGAAGACTG CTGGACACTA ATGTATCCTC TCTCGACTTT TGCAGCTCCA GATGGCGTGT TAGCAGGTGA GTCCTCTGTT CTTGTTCCCT TGGTGTATCA ACATGTCTGG GCATTGCTTT CCTCTCACTA TTTTCTTCGT CCCATCACTT CTGCTTTCTA ATGAGCATGA ATCIGTTCCT TGGCCAGACT ACTTTCCCTC TCCACCTTGC CTTGTCTTTC TTTTTTTCCC TGATTCATTG CATTCTCA AGTCATTCTC TCCTCTGTTT TAGTCAATAA CCATGTCTGT TGCACATATA CATGTCTCAT TCTCTCCT AGACACTTTG GCATGATCTC GCTCAATAAT TACATTATTA TTATTATTGC CATTITATAA TIGAGGATGC TGAAACTCAG TGATTITCTG GTGGTTACAT GGCTAAGGAA CTGGATTTCA ACGTAAGTTC CTTGGATCTA AGTCCAGTTC TCTTCTGACT ATATCACCCT TTTGTTATCA CCATGTATCT ACTTCTTTGG TCTCTGTTCA AATTTGCACT ACATCCCCTT GTTCCAGGAA GCCATTCAAG ACTGACTTTC TTAGTGCCTC TCACTACTTT CTGGAACTGA CATATGTTTT TCACTCTGTA TATACTTACA ATTAAATAGT CATAAATATT CAGAGCTTGG AGAAACCTTA TATTTCATCC AGTCCAGTAA ATTTATCCAT CCATAATTCA CTCATTCATT CACATAATAA ATATTTAATG TAACAATGGT TGAACATGGC AGACAGTGTT TCTACCTCAA AAGAGATTGC AGTCCTCATT TACAGATACT GAATTGAAAT TAACAGAAGT AGAGTGAGTC AGCTCAAATC 40 ACATAGTGAA TTGGTTTCTT TGTTTTTAAA TCTCCTGCAT ATGTGTCCTG TCTTTCTCCC TGTGTTGGGC GTTCCCTGGG GCAC'CAATAC TAATTTCTCC TTCCCCTAGA AATCAAAACA GGGTCTTATC ACCAACAGAA TAAGGACAGG TTGACCACTG ATTGTCAGAA TATTGCTTCG TTTGTACTTT TAAGCCTAGA CAGTTTTCAA TGACTTTTT TCTCTCTACA TGTCTTTCA TATTTTTATC TTCTTGAAGT CCCTCAGAAA CCTAAGGTCT CCTTGAACCC TCCATGGAAT AGAATATTTA AAGGAGAGAA TGTGACTCTT ACATGTAATG GGAACAATTT CTTTGAAGTC AGTICCACCA AATGGTTCCA CAATGGCAGC CTTTCAGAAG AGACAAATTC AAGTTTGAAT ATTGTGAATG CCAAATTTGA AGACAGTGGA GAATACAAAT GTCAGCACCA ACAAGTTAAT GAGAGTGAAC CTGTGTACCT GGAAGTCTTC AGTGGTAAGT TCCAGGGATA TGGAAATACA GATCTCTCAT GTGAGGGATG GCTCATCTGA AGA1GGGAAA AAACAGGTTA TTCCAAGGGT TAGGACACCA GAGTGGGATT CAAGGCCTCT CATTTTAAG ACCCCTGCAT TGGCTGGGCA CAGTGGCTCA CGCCTGTAAT CCCAGCACTT TGGGAGGCTG AGGCAGGTGG ATCACGAGGT CAGGAGATCG AGACCATCCG GCTAACATGG TGAAACCCCA TCTCTGCTAA AAAATATATA TATATAAAAT TAGCCGGGCG TAGTGGTGGG CACCTGTAGT CCCAGGTACT CGGGAGGCTG AGGCAGGAGA ATGGTGTGAA CCCAGGAGGT GGAGGTTGCA GTGAGCTGAG ATCACGCCAC TGCCCTCCAG CCTGGGCTAC AGAGCAAGAC TCCGTCTCAA AAAATAAATA AATAAATAAA AAAGACCCCT GCATCTCTTT TCTTCTACCC CCTTCCCTTT TGATTACTTG TATGCCTTCT TTCAATATTC TAGTCATCTC TCAATATTAT TCCTCCACCC TATITTCCTC TATCTTTTCT GCCTAGATTC AGGTATATAT TATGTGGTCA AACAGCATGA CATATATGTG AACATTTCAA AGAGCTGTGT ATCTGGAATA GGATCAAAAG GTTTGACTTA AAGTTTTGCT CTGCATAATC CATATGGCAG GACCTGAATA TTAGGTTGTA CTCTTCGTTA TGAAACATAT CTGGGTACAT TTCCTTATGT CCTCTGTTGT TACTTAAGAA CACATATTTC ATGCTTGTTT CATTTTTATC ACTCCTACTG CCAACAATA GCATAGCATG CTTAGGCACA TGTGGCTTAA TTAGCAAATG TTGAATAAAC AAATTAATGA TTTTGAATAG TGACCAATAG GTCTCTTTA TACTCTATAT TTTTCTCTTG AGTGAAAAAA AATGTTTCAA



	CCTCCATATG	ΤΑΑΛΤΤΟΟΑΑ	ΔCΔCΔΔΔCTΔ	AAGCAATGTA	GAATAGCTTC	<b>ምም ለ ምምር ር ር ጥ</b>	CCACTACCTT
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	FI TACTA ACAC	TIAAF.IGGGA TI	TAAAGTTC-3′ (F)	RAG. NO:_)(SEQ.	ID NO:2501)		
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10		' (FEAG. NO:					
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	CACACCCGCC	TTATTCGTAT	ACNCATTTAA	TTCTGAGAAG	CACTCTATAG	AAAATAAGAA	TAAGAAAATA
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25	GGGTTAAAAG	GACACATTGA	AAACAAGAAG	C TCATTGTGGC	TTTTTTTCC	TCCTTTTTGA	ACAGTTTTCT
	ATTTCTGGAA	TGT1GTCAAT	TATATCTGAA	AGGAGAAATG	CAACATATCT	GGTGAGTTGC	CCGTTTCTGT
	CTTTGTCCAT	CCTTGAAAAG	ATAAGAAGAA	CAGAGTTTTA	AGAGTCTTAA	GGGAAACACA	TCTTTGTCTC
	CTATATTACT	TGTC AATGTG	GATATATGAT	TTTGTTTCAA	TCTATTTTGT	GTCCTAAGGC	TTTTTGCAAC
	AGAAGTTGGA	TATATCATTA	GAAACATAAA	TTGTACCATT	TAACATACAT	GAAGTTTATG	TTTACCTTGA
30	CGTTCTTCTA	AAAA.GTGTCC	TACACCGGCA	TTGTCCTTGT	AGGCATATTC	ACATGATCAA	ATAAAATAAT
	TAGTTTTCAA	TTAAGGAGAA	TATTTGAGGA	AAGACCGTAC	GTGTTCATGT	GGTTCCTGAA	GGCAGTCCAG
	TGAGAAAGTA	ATA'TATGCTT	CATTAAACAA	TGCGGACATT	TTCAGGGTTT	CCCTTTTTAA	CCAAAATTTG
	GAAGCAATGT	GGAATTTACT	GGATGCATCC	AGCCCTGAAA	TGAAGATAGG	TTTATTGAAT	GTGCCAGCAA
	GTGCAGGCCC	AGG CTGAGT		ATTATCAGGT	GAGAGGAAGC	CTGGGAGCAA	ACACTGCCAG
35	CAGCATAGCT	GGGGGAACGG	GAATTACCAT	CCTGATCATC	AACCTGAAGA	AGAGCTTGGC	CTATATCCAC
	ATCCACAGTT	GCCAGAAATT	TTTTGAGACC	AAGTGCTTTA	TGGCTTCCTT	TTCCACTGTA	TGTATTTTT
	TTTGTGTGGG	AAGACTAAGA	TTCTGGGTCC	TAATGTAAGT	AAGAAGCCCT	CTTCTCCTGT	TCCATGAACA
	CCATCCTTTT		TATTACACAG	TATAGTGGTT	CTGTAAGTTC	ACACAGCCCA	GGGAGATGCT
40	GGCTGCCCAC	TCCCCTCAAC	CCAGGCAAAT	TCCTCGGGGT	TAAAGTTATC	TACTGCAAGT	GACGATCTCT
40	GGGTTTTTCT	GTGC CTGTGT	TTGTGTGTGT	GTGTGTGTGT	GTGTGTGTGT	GTATGTGTCA	CTTTAAAAGG
	ACTGGTCAGA	TGGTAGGGAG			AAGAAAATAA		CGAATACCAA
	TGTGACTCTT	TTTGTTTGTC	ATTTGTTGCT	GTTCAATAGG	AAATTGTAGT	GATGATGCTG	TTTCTCACCA
						GAACTCAAAG	
15						TTTATTCCTT	
45						TACTTTGGTT	
						CTCTGAATGA	
						TGGATGTACA	
						CCTATTCCTG	
50	ATTCCTTTGT				AAACCTCAGT		TTCTGATTCA
30						AGAACCACCA	
	CTCTACCCAC	GCCCAIGICI	GATGGAAGAA	ACATACICIC	TCCATCTGTC	CACTTTCCTG	AGGCATTCAA
	GTCACCCTCA	CCACCCCCCA	TCACTCTCCTC	CAGGCTGGGC	ACGGTGTCAC	GCCTGTAATC	TCAGCACTTT
	ATCTTCTTCA	ATTARA COA	TCACTTGAAG	TCAGGAGTTC	AAAACCAGCC	TGGCCAAATG	GCAAAACCAA
55						CAACAAAACA	
55	CTCAACCACC	ACA PROCOTE	CACCCCA	GATGGAGGT	AGGTACCTGA	GGTTCCAGAT	ACTIGGGAGG
						GAGATCATGC	
	GATTTCCACA	CCACCCTGGG	CAACATCCTC	AAACTCCCTC	TOTACTAAAA	GAAGAATAAT	TACTCCCCCC
						ATATAAAACT	
60						ATTGCTTGAA CATAGTGAGA	
00						TAAGACAGCA	
						CTTGGCCAGC	
	Sommer	OHOLMACI I U	TOTALIGACIO	ACATUATTIC	TTTTOUCCCA	CITOUCCAUC	INGICIOGII



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		GAAATGAAAG					
	TAGATGAGGT			CTAGGGATGG		GTGATTGATA	TGAAATGATT
	TTTCCCTTAT	CAGC TTCCAG	AGGATCGTGT	TTATGAAGAA	TTAAACATAT	ATTCAGCTAC	TTACAGTGAG
_	TTGGAAGACC	CAGGGGAAAT		ATTGATTTAT	AAGAATCACG	TGTCCAGAAC	ACTCTGATTC
5	ACAGCCAAGG			GTTAAGGGGC			TCTCCACAGC
	CTGCTGGTTT	TACATTAGAT	TTATTCGCCT	GATAAGAATA	TTTTGTTTCT	GCTGCTTCTG	TCCACCTTAA
	TATGCTCCTT	CTATTTGTAG	ATATGATAGA	CTCCTATTTT	TCTTGTTTTA	TATTATGACC	ACACACATCT
	CTGCTGGAAA	GTCAACATGT	AGTAAGCAAG	ATTTAACTGT	TTGATTATAA	CTGTGCAAAT	ACAGAAAAAA
	AGAAGGCTGG	CTG AAAGTTG	AGTTAAACTT	TGACAGTTTG	ATAATATTTG	GTTCTTAGGG	TTTTTTTTT
10	TTTTAGCATT	CTTAATAGTT	ACAGTTGGGC	ATGATTTGTA	CCATCCACCC	ATACCCACAC	AGTCACAGTC
	ACACACACAT	ATG' [ATTACT	TACACTATAT	ATAACTTCCT	ATGCAAATAT	TTTACCACCA	GTCAATAATA
	CATTTTTGCC	AAGA.CATGAA	GTTTTATAAA	GATCTGTATA	ATTGCCTGAA	TCACCAGCAC	ATTCACTGAC
	ATGATATTAT	TTGC AGATTG	ACAAGTAGGA	AGTGGGGAAC	TTTTATTAAG	TTACTCGTTG	TCTGGGGAGG
	TAAATAGGTT	AAAAACAGGG	AAATTATAAG	TGCAGAGATT	AACATTTCAC	AAATGTTTAG	TGAAACATTT
15	GTGAAAAAAG	AAG ACTAAAT	TAAGACCTGA	GCTGAAATAA	AGTGACGTGG	AAATGGAAAT	AATGGTTATA
		GTAGAAAAAG					TAGACAAGCA
	ACTGGTTGAC		AGCGTTTGAG	TCTAAGATGA	AAGGAGAACA	CTGGTTATGT	TGATAGAATG
	ATAAAAAGGG	TCGGGCGCGG	AGGCTCACGC		AGCCCTTTGG		TGGGCAGATC
						TCTACTAAAA	
20		GGGTGTGGTG				GGATGAGGCA	
		GAGGCGGAGG					
		CTCAAAAAA					
		GACCTAAATT	AAGTCTCATT		GATTTTGGGG		AAATGCAGCC
	ATAGAGGGCC	TGATGACATC		GTTCTGGTAA		TGATACACGG	TTTGGTGTCA
25	TTATAAGAGA	AATCATTATT			CTAAGAGAAT	TATTTTGAGA	TAGAAGTGAA
23					CTAAGGATAA		
		ATA# ACATGC					AGAAGATACA
		AAGTATCCAT				GAAAAGTCCA	
	CAACTCCACC			GAGAAAACAG			
30		ACATGAGTAT		TAAATGAATA		TGAATGCAAA	
50		TATGTGCGAA					AGAGAAAGAG
						TGAAGAAAAG	
	AAAAATTCTG	TTTATAAAAG		TAGTTTATGT	TTTTAGCCTA	AGTATAAGAG	TCCTACAGAT
	GGACTGAAAA	AAA CCTCAC	GAGAGTATTA		ATGAAATAAT	TACATTTTAT	GTATTGAGGA
25	TGCCAAGATT	AAAAGGTGAC	AGGTAGATGT	TAATTTCCCT		AGTGATCACG	ACAATCACAC
35	AACAAATAAT	TAA GTGACTT	GGTATGCTTT	ATTTAATTGT	AGGGCCTGAG	GTTTTCCATT	CTCATTTTTC
	TAAAATACAA	TTTTGTTTCT	CCAAATTTGA	CAGCAGAATA	AAAACCCTAC	CCTTTCACTG	TGTATCATGC
	TAAGCTGCAT	CTCTACTCTT	GATCATCTGT	AGGTATTAAT	CACATCACTT	CCATGGCATG	GATGTTCACA
	TACAGACTCT	TAACCCTGGT	TTACCAGGAC	CTCTAGGAGT	GGATCCAATC	TATATCTTTA	CAGTTGTATA
40	GTATATGATA	TCTCTTTTAT	TTCACTCAAT	TTATATTTTC	ATCATTGACT	ACATATTTCT	TATACACAAC
40	ACACAATTTA	TGAATTTTTT	CTCAAGATCA	TTCTGAGAGT	TGCCCCACCC	TACCTGCCTT	TTATAGTACG
	CCCACCTCAG	GCAGACACAG	AGCACAATGC	TGGGGTTCTC	TTCACACTAT	CACTGCCCCA	AATTGTCTTT
	CTAAATTTCA	ACT1 CAATGT	CATCTTCTCC		CTGAATGAAC	ACCTTTTCAT	CCAGCCTTAA
		CATAACTACT	CTATCCCACG	ATGCAGTATT	GTATCATTAA		GCTTGTGACC
	TCCTTATGTA	TTCTCAATTA	CCTGTATTTG	TGCAATAAAT	TGGAATAATG		TCTTATCTGT
45		GCATGCAAGA					
		AGA/3CAGTTT					
		CCAGAAAACA					
	AACAGAATGT	AAGGACAATC	ACCAGCCATC	TTTTGTCAAT	AATTGATGGA	ATAGAGTTGA	AAGGAACTGG
	AGCATGAGTC	ATA' TTGACC	AGTCAGTCCT	CACTCTTATT	TACTTGCTAT	GTAAACTTGA	GAAAGCTTTT
50	TTCTCTTTGT	GAACCTCAGG	TTTTACATCT	GAAAATGAGA	AATTTGGAAC	AAAAGATTCC	TAACTGGTCT
	TTCTGTTCCC	ATATTCTGTG	ATTTTTCAAT	ATTTAGGATT	TTTGGTAATC	ACAATTACTT	AGTTTGTGGT
	TGAGATAGCA	ACACGAATCA	GAACTATTTG	GTGGACATAT	TTTCAAAGGA	GTAGCTCTCC	ACTTTGGGTA
		GCNGGTCGTG					
		AGGAGATCGA					
55		GGCCTGGTGG					
		AGGCGGAGCT					
		TCAAAAAAA					
		CTAAATCCCT					
		CTTT GGGAGA					
60		AAAAATACTA					
		CTGGAGAATC A					



### Human Histidine L'ecarboxylase Nucleic Acid and Antisense Oligonucleotide Fragments

- 5 5'-GGC TCT GGC (FRAG. NO:1701) (SEQ. ID NO: 1712)
  - 5'-CCC TTG G (FRAG. NO:1702) (SEQ. ID NO: 1713)
  - 5'- TT TGT TCT TCC (FRAG. NO:1703) (SEQ. ID NO: 1714)
  - 5'- TCT CCC TTG GGC TCT GGC TCC TTC TC-3' (FRAG. NO:1024) (SEO. ID NO: 1034)
  - 5'- TCT CTC TCC CTC TCT CTC TGT -3' (FRAG. NO:1025) (SEQ. ID NO:1035)
- 10 5'- CGC CTC CGC CCI GGC TGC TGG GGT GGT GGT GC-3' (FRAG. NO:1026) (SEQ. ID NO:1036)
  - 5'- TTT TGT TCT TCC TTG CTG CC-3' (FRAG. NO:1027) (SEQ. ID NO:1037)
  - 5'- GCC CCG CTG CTT GTC T TC CTC G-3' (FRAG. NO:1028) (SEQ. ID NO:1038)
  - 5'-CTC TGT CCC TCT CTC TCT GTB CTC CTC BGG CTC CBT CBT CTC CCT TGG GC (FRAG.NO:1029)(SEQ.ID NO:1039)

#### Human Beta Tryptase Nucleic Acid and Antisense Oligonucleotide Fragments

- - 5'- GCT CCT GGG GGC CT-3' (FRAG. NO:1705) (SEQ. ID NO: 1716)
  - 5'-CGT BGG CGC-3' (FRAG. NO:1706) (SEQ. ID NO: 1717)
- 20 5'-T GGC CTG GGG-3' (FRAG. NO:1707) (SEQ. ID NO: 1718)
  - 5'-CTT GCT CCT GGG GGC CTC CTG-3' (FRAG. NO:1030) (SEQ. ID NO:1040)
  - 5'-GTC CCT CCG GGT GTT CCC GGC-3' (FRAG. NO:1031) (SEQ. ID NO:1041)

# 25 <u>Human Tryptase-I Nucleic Acid and Antisense Oligonucleotide Fragments</u>

5'-CTT GCT CCT GGG GGC CTC CTG GTC CCT CTG GCT G TT CCC GGC CCT GGB CTG GGG CBG GGG CCG CGT BGG CGC GGC TCG CCB GGB CGG GCB GCC GCB GCB GCC GCC TCB GCC TCG CCC CGG BBT TCC-3' (FRAG. NO: 1708) (SEQ. ID NO:1719)

- 5'-CT CCT GGG GGC CTC CTG-3' (FRAG. NO:1709) (SEQ. ID NO:1720)
- 30 5'-B TCC TGG CCB CGG BBT TCC -3' (FRAG. NO:1710) (SEQ. ID NO:1721)
  - 5'-GTC CCT C-3' (FRAG. NO:1711) (SEQ. ID NO:1722)
  - 5'-CTT GCT CCT GGG GGC CTC CTG-3' (FRAG. NO:1033) (SEO. ID NO:1043)
    - 5'-GTC CCT CTG GCT G TT CCC GGC-3' (FRAG. NO:1034) (SEQ. ID NO:1044)
- 35 TCB GCB TCC TGG CCB CGG BBT TCC -3' (FRAG. NO:1035) (SEO. ID NO:1045)

#### Human Prostaglan lin D Synthase Nucleic Acid and Antisense Oligonucleotide Fragments

- 40 5'-T TCT CCT GCB GCC GBG -3' (FRAG. NO:1713) (SEQ. ID NO:1724)
  - 5'-CTT GCT GCC CTG GCT GT-3' (FRAG. NO:1714) (SEQ. ID NO:1725)
  - 5'- TCT TCT CCT GG-3' (FRAG. NO:1715) (SEQ. ID NO:1726)
  - 5'-GGT GTG CGG GGC CTG GTG CC-3' (FRAG. NO:1036) (SEQ. ID NO:1046)
  - 5'-CCT GGG CCT CGG GTG CTG CCT GT-3' (FRAG. NO:1037) (SEQ. ID NO:1047)
- 45 5'-GCG CTG CCT TCT TCT CCT GG-3' (FRAG. NO:1038) (SEQ. ID NO:1048)
  - 5'-GTC CTC GCC GGG GCC CTT GCT GCC CTG GCT GT-3' (FRAG. NO:1039) (SEQ. ID NO:1049)
  - 5'-GCC CTG GGG GTC TGG GTT CGG CTG T-3' (FRAG. NO:1040) (SEQ. ID NO:1050)
  - 5'-CCC CBG CBG GBC CBG TCC CBT CCB CBG CGT GTG BTG BGT BGC CBT TCT CCT GCB GCC GBG -3' (FRAG. NO:1041) (SEQ. ID NO:1051)

## 50 Human Cyclooxygenase-2 Nucleic Acid and Antisense Oligonucleotide Fragments

5'-GGG CGC GGG CGB GCB TCG C TTT GGG CTT TTC TCC TTT GGT T TGB GCG CCB GGB CCG CGC BCB GCB GCB GGG CGC GGG CGB GCB CGC GGG CGG GCB GGG-3' (FRAG. NO: 1716) (SEQ. ID NO:1729)

- 5'-G GCB GGG -3' (FF:AG. NO: 1717) (SEQ. ID NO: 1730)
- 5'-TCC TTT GGT T-3' (FRAG. NO:1718) (SEQ. ID NO:1731)
- 55 5'- GGG CGC GGG CGB GCB TCG C-3' (FRAG. NO:1042) (SEQ. ID NO:1052)
  - 5'- TTT GGG CTT TTC TCC TTT GGT T-3' (FRAG. NO:1043) (SEQ. ID NO:1053)
  - 5'-TGB GCG CCB GGB CCG CGC BCB GCB GCB GGG CGC GGG CGB GCB TCG CBG CGG CGG GCB GGG -3' (FRAG. NO:1044) (SE(). ID NO:1054)



### Human Eosinophil Cationic Protein Nucleic Acid and Antisense Oligonucleotide Fragments

5'-CCT CCT TCC TGG TCT GTC TGC CBG BCB BBT TTG GGB BGT GBB CBG TTT TGG BBC CBT GTT TCC CBG TCT CTG BGC TGT GGC-3' (FRAG. NO: 1719) (SEQ. ID NO: 1732)

- 5'-TTC TCC TTT GGT I-3' (FRAG. NO:1720) (SEQ. ID NO: 1733)
- 5'-T TTC TCC TTT GGT T-3' (FRAG. NO:1721) (SEQ. ID NO:1734)
  - 5'- GGG CGC GGG CGB GCB TCG C-3' (FRAG. NO:1042) (SEQ. ID NO:1052)
  - 5'- TTT GGG CTT TTC TCC TTT GGT T-3' (FRAG. NO:1043) (SEQ. ID NO:1053)
  - 5'-TGB GCG CCB GGB CCG CGC BCB GCB GCB GGG CGC GGG CGB GCB TCG CBG CGG CGG GCB GGG -3' (FRAG. NO:1044) (SE(). ID NO:1054)

## 10 <u>Human Eosinophil Derived Neurotoxin Nucleic Acid and Antisense Oligonucleotide Fragments</u>

- 5'-TTC CTG T-3' (FRAG. NO:1723) (SEQ. ID NO: 1736)
- 15 5'-CTC TTT CTG CT-3' (FRAG. NO: 1724) (SEQ. ID NO:1737)
  - 5'-CCC CTT CTG TCC C-3' (FRAG. NO:1725) (SEQ. ID NO: 1738)
    5'- GCC CTG CTG CTC TTT CTG CT-3' (FRAG. NO:1047) (SEO. ID NO:1055)
  - 5'- TCC CTT GGT GGC TTG GGC C-3' (FRAG. NO:1048) (SEQ. ID NO:1056)
  - 5'- GCT GGT TGT TCT GGG GTT C-3' (FRAG. NO:1049) (SEQ. ID NO:1058)
  - 5'- TTG CTG CCC CTT CTG TCC C-3' (FRAG. NO:1050) (SEQ. ID NO:1057)
- 5'- TGT TTG CTG GTG TCT GCG C -3' (FRAG. NO:1050) (SEQ. ID NO:1057)
  - 5'- CCC CBB CBG BBG BBG CBG BCB BBT TTG GGB BGT GBB CBG TTT TGG BBC CBT GTT TCC TGT-3' (FRAG. NO:1052) (SEO. ID NO:1060)

### Human Eosinophil Peroxidase Nucleic Acid and Antisense Oligonucleotide Fragments

TCT TGT TTT GGG GGC CGC GGC CGT TGT CTT G GTT TGG GGG TTT CCG TTG GGG TTC TCC TGG CCC GTC TTT GGT G 5'-GCB CCG TCC BGT GBT GGT GCG GTB CTT GTC GCT GCB GCG CTC GGC CTG GTC CCG GBG BGC CACCGCTCCT GTCAGCCAAC AAATATCCAT TGAGCGACAC CTGTGTCCCA GGTGCTGCTC TGGGCCCTGG GAGAAGTGCA TCAGTGGGCT TGGTAGTAGA GGGTAGGGAT GGAGTGAAGG GTAGGCAGGA AGAATGTCCC CAGGCTGGTA GGAGGTGGGG TGGGGGGTTT CAGTCTCAAA ACTCCCATGA AAACCAGAGA GAAGTTTCAG AACTCCACCC AAGAGGCTGG GTTTCTAGGG CCCAGAGCTG CCCTCCCCCA CCCTAGAATG GGCTATAAAA GTCCCTTCCC AGCTACGTCC AGAGAAGAGC TGGAGGAAGT GAGAGGTCGG CTGGGGGTCC TCAAAGTGAG AGGGGAGCAG AGGATCCTCC CGTGCAGGCT GTGGATGTCA CTCACTTCCC AGCTGGTGAA GCCTCGCTGC AGAGATGCAT CTGCTCCCAG CCCTGGCAGG GGTCCTGGCC ACACTCGTCC TCGCCCAGCC CTGTGAGGGC ACTGACCCAG GTA/TAGTCC CCTAGACAGG CAAGGAGGAG GGAGGGGAAA TGGAAGGGGA AGCACTTGGG TCTTGGAGGG GGTCTTGTGG CTTGCTGAAC CCTGAGTCCC CATCTCTTTG AACAGCCTCC CCTGGGGCAG TGGAGACCTC GGTCCTGCGA GACTGCATAG CAGAGGCCAA GTTGCTGGTG GATGCTGCCT ACAATTGGAC CCAGAAGAGG TGGACTTGGG TCTGGGGGCT GCATGGGCCT GGGAGGATCA GT TAATACCTTG TGGGGTCAGG GAGCCCATGT CCCGTGCTGA TGTTATTTCC CCACCAGGTC CGGGCTGTCT CCAACCAGAT TGTGCGCTTC CCCAATGAGA GACTGACCTC CGACCGTGGC CGAGCCCTCA TGTTCATGCA GTGGGGCCAG TTCATTGACC ATGACCTGGA CTTCTCCCCG GAGTCCCCGG CCAGAGTGGC CTTCACTGCA GGCGTTGACT GTGAGAGGAC CTGCGCCCAG CTGCCCCCCT GCTTTCCCAT CAAGGTACCT ACCCTCAGCC AATCTCCCAT GCCCTTGTGT GGCCTCCCCC AAAGGCAAGG TGCTGGGGGT GGGGATCTGG AAGACTGGAG CACCATCCTT AAGGAGCTGC CTGTGGAGCT AGGGTATGAG ACAGAGACAC AAG CACTGTCTCC TCTTCCATCT CAGATCCCAC CCAATGACCC CCGCATCAAG AACCAGCGTG ACTGCATCCC TTTCTTCCGC TCGGCACCCT CATGCCCCCA AAACAAGAAC AGAGTCCGCA ACCAGATCAA CGCGCTCACC TCCTTTGTGG ACGCCAGCAT GGTGTATGGC AGTGAGGTCT CCCTCTCGCT GCGCCTCCGC AACCGGACCA ACTACCTGGG GCTGCTGGCC ATCAACCAGC GCTTTCAAGA CAACGGCCGG GCCCTGCTGC CCTTCGACAA CCTGCACGAT GACCCCTGTC TCCTCACCAA CCGCTCGGCG 50 CGCATCCCCT GCTTCCTGGC AGGTCAGACA GGGAGGAAGG TGGTGTCTTC CCAGGAAACA GCCATCCCTG GGGTCCCAAC TGGGAAGCAA TGGTGGGATG TGGTGAAGGT ACATGGTTTG GGACCTCAGT ATTAGGCACA CCATAAGCAT GGATCTGTGC AC TGAAGAGATG GAGGTCCAGT GAGGGCCAGG AGTTTGGCCC ACCCCGTCTC TCCCATCCCC AGCCCTGGGT CTACCCTGGT AGAAAGACAT TTCTCTGGGA AAGGCTGCAG TAAATCTGAG CTTGGGGTTT TCAAGGTGAC ACCCGATCAA CGGAAACCCC CAAACTGGCA GCCATGCACA CCCTCTTTAT GCGAGAGCAC AACCGGCTGG CCACCGAGCT GAGACGCCTG AATCCCCGGT GGAATGGAGA CAAACTGTAC AATGAGGCTC GGAAGATCAT GGGGGCCATG GTCCAGGTAA GGAGCTCTGC ATCCCAGCAT CCCC CTTTGTATCT CCACCCACCA ATAGTAAATT AATGTTGTCA CATTTGACGT GATGACAATA AAGAATATGT CTGAGCCACC CTTTGAAAAG GCAAGGGTAT GGGTGAGTAG CCTCTGGGGA ATGTTCCTCC TGTCTTCCCT TCCAGATCAT CACCTACCGA GACTTCTGC CCCTGGTTCT GGGCAAGGCC CGGGCCAGGA GAACCCTGGG GCACTACAGG 60 GGGTACTGCT CCAATGTGGA CCCACGGGTG GCCAATGTCT TCACCCTGGC CTTCCGCTTT GGCCACACAA



	TGCTCCAGCC				GGCCTCCGCA		ATGTCCCACT
						TTTTCCAGGG	
	GGTGAGGGTG					CT CCAGAACTCT	GTTTCCTGAC
	AAACGTTACT				GCTAGCTTGG		TAACCCAAGT
5	AGCTTCCCAG	AGGCTGGTCC			CCTGCCACCA	GGGGGCATCG	ACCCCATCCT
	CCGGGGCCTC	ATGGCCACCC	CTGCCAAGCT	GAACCGTCAG	GATGCCATGT	TAGTGGATGA	GCTCCGGGAC
	CGGCTGTTTC	GGC/AGTGAG	GAGGATTGGG			CATGCAACGA	AGCCGGGACC
	ACGGCCTTCC	AGGTGAGGGG	GCTGTCCACC				CTCAAGGGGT
	TCTGGGAAGA	CCCT'GGTACC			GTGGCAGAAA	CGAGGTGTTT	TCACCAAAAG
10	ACAGCGCAAG	GCCCTGAGCA	GAATTTCCTT	GTCTCGAATT	ATATGTGACA	ATACCGGTAT	CACCACGGTT
	TCAAGGGACA	TCT CAGAGC	CAACATCTAC			CAGCCGTATC	CCCAGGTTGA
	ACCTATCAGC	CTGCCGAGGG	ACATGAGGCT	TCTGCAGGTA	AGGGGAGGCC	ACCTCCAGCA	CCCTGGGCTG
	GTTAAGCCTC	ACAT'CCTTCC	CTGGATGGAT	GGCTGAGTCC	TCTTAGGTCT	CTAAGCAGAG	AAAACAGAAC
	TTGTCACTAG	GTACTCTTTC	CAAGTGGCTT	CCCAATGTGC	TAGTTTCTGG	GCTGACAGTC	AATTCCAGGC
15	CCTAGGACTT	TGGGGGAAA				GCCAGGACCC	CTGCCAGGGC
	ACTGACCCAG	CCTCCCCTGG	GGCAGTGGAG	ACCTCGGTCC	TGCGAGACTG	CATAGCAGAG	GCCAAGTTGC
	TGGTGGATGC	TGCCTACAAT	TGGACCCAGA	AGAGCATCAA	GCAGCGGCTT	CGCAGCGGTT	CAGCCAGCCC
	CATGGACCTC	CTG1'CCTACT	TCAAACAACC	GGTAGCAGCC	ACCAGGACAG	TTGTTCGGGC	CGCAGATTAT
	ATGCATGTGG	CTT1'GGGGCT	GCTTGAAGAG	AAGTTACAAC	CCCAGCGGTC	CGGACCCTTC	ATTGTCACTG
20	ATGTGCTAAC	AGAACCACAG	CTGCGGCTGC	TGTCCCAGGC	CAGTGGCTGT	GCTCTCCGGG	ACCAGGCCGA
	GCGCTGCAGC	GACAAGTACC	GCACCATCAC	TGGACGGTGC	AACAACAAGA	GGAGACCCTT	GCTAGGGGCC
	TCCAACCAGG	CTCTGGCTCG	CTGGCTGCCC	GCCGAGTATG	AGGATGGGCT	GTCGCTCCCC	TTCGGCTGGA
	CCCCCAGCAG	GAG 3CGCAAT	GGCTTCCTTC	TCCCTCTTGT	CCGGGCTGTC	TCCAACCAGA	TTGTGCGCTT
	CCCCAATGAG	AGACTGACCT	CCGACCGTGG	CCGAGCCCTC	ATGTTCATGC	AGTGGGGCCA	GTTCATTGAC
25	CATGACCTGG	ACTT'CTCCCC	GGAGTCCCCG	GCCAGAGTGG	CCTTCACTGC	AGGCGTTGAC	TGTGAGAGGA
	CCTGCGCCCA	GCTGCCCCCC	TGCTTTCCCA	TCAAGATCCC	ACCCAATGAC	CCCCGCATCA	AGAACCAGCG
	TGACTGCATC	CCTTTCTTCC	GCTCGGCACC	CTCATGCCCC	CAAAACAAGA	ACAGAGTCCG	CAACCAGATC
	AACGCGCTCA	CCTCCTTTGT	GGACGCCAGC	ATGGTGTATG	GCAGTGAGGT	CTCCCTCTCG	CTGCGGCTCC
	GCAACCGGAC	CAACTACCTG	GGGCTGCTGG	CCATCAACCA	GCGCTTTCAA	GACAACGGCC	GGGCCCTGCT
30	GCCCTTCGAC	AACCTGCACG	ATGACCCCTG	TCTCCTCACC	AACCGCTCGG	CGCGCATCCC	CTGCTTCCTG
	GCAGGTGACA	CCCGATCAAC	GGAAACCCCC	AAACTGGCAG	CCATGCACAC	CCTCTTTATG	CGAGAGCACA
	ACCGGCTGGC	CACCGAGCTG	AGACGCCTGA	ATCCCCGGTG	GAATGGAGAC	AAACTGTACA	ATGAGGCTCG
	GAAGATCATG	GGGGCCATGG			GACTTTCTGC		GGGCAAGGCC
	CGGGCCAGGA	GAACCCTGGG	GCACTACAGG	GGGTACTGCT	CCAATGTGGA	CCCACGGGTG	GCCAATGTCT
35	TCACCCTGGC	CTT('CGCTTT	GGCCACACAA		CTTCATGTTC	CGCTTGGACA	GTCAGTACCG
	GGCCTCCGCA	CCCAACTCGC	ATGTCCCACT	TAGCTCTGCC	TTCTTTGCCA	GCTGGCGGAT	CGTGTATGAA
	GGGGGCATCG	ACCCCATCCT	CCGGGGCCTC	ATGGCCACCC	CTGCCAAGCT	GAACCGTCAG	GATGCCATGT
	TAGTGGATGA	GCTCCGGGAC	CGGCTGTTTC		GAGGATTGGG	CTGGACCTGG	CAGCTCTCAA
	CATGCAACGA	AGCCGGGACC	ACGGCCTTCC	AGGGTACAAT	GCTTGGAGGC	GCTTCTGTGG	GCTCTCCCAG
40	CCCCGGAATT	TGGCACAGCT			AGGACTTGGC	AAGGAAGTTC	CTGAATTTGT
	ATGGAACACC	TGACAACATT	GACATCTGGA	TTGGGGCCAT	CGCTGAGCCT	CTTTTGCCGG	GGGCTCGAGT
	GGGGCCTCTT	CTGC CTTGTC	TGTTCGAGAA	CCAGTTCAGA	AGAGCCGAGA	CGGAGACAGG	TTCTGGTGGC
	AGAACGAGGT					CTTGTCTCGA	ATTATATGTG
						TACCCTCGGG	
45						GCTTCTGCAG	
						CTTGTCTCCC	
						CCAGGAGTGA	
						TATGAATCAG	
						CAGCTGGAGG	
50						ACCACTCGGT	
						TTCTACCAAT	
			(SEQ. ID NO: 30				
					CTGTGTCCCA	GGTGCTGCTC	TGGGCCCTGG
						GTAGGCAGGA	
55						AAACCAGAGA	
						CCCTAGAATG	
						CTGGGGGTCC	
						AGCTGGTGAA	
						TCGCCCAGCC	
60						TGGAAGGGGA	
						AACAGCCTCC	
						GATGCTGCCT	



CCAGAAGAGG TGG/1CTTGGG TCTGGGGGCT GCATGGGCCT GGGAGGATCA GT-3' (FRAG. NO:\_)(SEQ. ID NO:2483)

5'-TAATACCTTG TGGGGTCAGG GAGCCCATGT CCCGTGCTGA TGTTATTTCC CCACCAGGTC CGGGCTGTCT CCAACCAGAT TGTCCGCTTC CCCAATGAGA GACTGACCTC CGACCGTGGC CGAGCCCTCA TGTTCATGCA GTGGGGCCAG TTCATTGACC ATGACCTGGA CTTCTCCCCG GAGTCCCCGG CCAGAGTGGC CTTCACTGCA GCCGTTGACT GTGAGAGGAC CTGCGCCCAG CTGCCCCCCT GCTTTCCCAT CAAGGTACCT ACCCTCAGCC AATCTCCCAT GCCCTTGTGT GGCCTCCCCC AAAGGCAAGG TGCTGGGGGT GGGGATCTGG AAGACTGGAG CACCATCCTT AAGCAGCTGC CTGTGGAGCT AGGGTATGAG ACAGAGACAC AAG-3' (FRAG.NO: )(SEQ.ID NO:2484)

5'-CACTGTCTCC TCTTCCATCT CAGATCCCAC CCAATGACCC CCGCATCAAG AACCAGCGTG ACTGCATCCC TTTCTTCCGC TCGGCACCCT CATGCCCCCA AAACAAGAAC AGAGTCCGCA ACCAGATCAA CGCGCTCACC TCCTTTGTGG ACGCCAGCAT GGTGTATGGC AGTGAGGTCT CCCTCTCGCT GCGGCTCCGC AACCGGACCA ACTACCTGGG GCTCCTGGCC ATCAACCAGC GCTTTCAAGA CAACGGCCGG GCCCTGCTGC CCTTCGACAA CCTGCACGAT GACCCCTGTC TCCTCACCAA CCGCTCGGCG CGCATCCCCT GCTTCCTGGC AGGTCAGACA CGGAGGAAGG TGGTGTCTTC CCAGGAAACA GCCATCCCTG GGGTCCCAAC TGGGAAGCAA TGGTGGGATG TGGTGAAGGT ACATGGTTTG GGACCTCAGT ATTAGGCACA CCATAAGCAT GGATCTGTGC AC-3' (FRAG.NO: )(SEQ.ID NO:2485)

5'-TGAAGAGATG GAGGTCCAGT GAGGGCCAGG AGTTTGGCCC ACCCCGTCTC TCCCATCCCC AGCCCTGGGT CTACCCTGGT AGA/AGACAT TTCTCTGGGA AAGGCTGCAG TAAATCTGAG CTTGGGGTTT TCAAGGTGAC ACCCGATCAA CGG/AAACCCC CAAACTGGCA GCCATGCACA CCCTCTTTAT GCGAGAGCAC AACCGGCTGG CCACCGAGCT GAG/ACGCCTG AATCCCCGGT GGAATGGAGA CAAACTGTAC AATGAGGCTC GGAAGATCAT GGGGGCCATG GTCC/AGGTAA GGAGCTCTGC ATCCCAGCAT CCCCC-3' (FRAG.NO: )(SEQ.IDNO:2486)

5'-CTTTGTATCT CCACCCACCA ATAGTAAATT AATGTTGTCA CATTTGACGT GATGACAATA AAGAATATGT CTGAGCCACC CTTTGAAAAG GCAAGGGTAT GGGTGAGTAG CCTCTGGGGA ATGTTCCTC TGTCTTCCCT TCCAGATCAT CACCTACCGA GACTTTCTGC CCCTGGTTCT GGGCAAGGCC CGGGCCAGGA GAACCCTGGG GCACTACAGG GGGTACTGCT CCAATGTGGA CCCACGGGTG GCCAATGTCT TCACCCTGGC CTTCCGCTTT GGCCACACAA TGC'CCAGCC CTTCATGTTC CGCTTGGACA GTCAGTACCG GGCCTCCGCA CCCAACTCGC ATGTCCCACT TAGC'TCTGCC TTCTTTGCCA GCTGGCGGAT CGTGTATGAA GGTGACCAGG TTTTCCAGGG GGCAAATGGG GGTGAGGGTG GGGAGCATGC CCTCCCCTAG GTGG-3' (FRAG.NO: )(SEQ.ID NO:2487)

5'-TCCAGCTGCT TCATGTCTCT CCAGAACTCT GTTTCCTGAC AAACGTTACT AACATACCCG ACTGGCTTGT CCAGCTCTGG GCTAGCTTGG CATCATGTGA TAACCCAAGT AGCTTCCCAG AGGCTGGTCC AATCTGTGCT GCTCACATTC CCTCCCACCA GGGGGCATCG ACCCCATCCT CCGGGGCCTC ATGGCCACCC CTGCCAAGCT GAACCGTCAG GATGCCATGT TAGTGGATGA GCTCCGGGAC CGGCTGTTC GGCAAGTGAG GAGGATTGGG CTGGACCTGG CAGCTCTCAA CATGCAACGA AGCCGGGACC ACGGCCTTCC AGGTGAGGGG GCTGTCCACC

35 TCTTCTCCCA GCTTT 3CTCG GGCCAGGCTG CTCAAGGGGT TCTGGGAAGA CCCTGGTACC-3' (FRAG.NO:\_)(SEQ.ID NO:2488)
5'-CGACTGCCTG GTAGGTTCTG GTGGCAGAAA CGAGGTGTTT TCACCAAAAG ACAGCGCAAG GCCCTGAGCA

GAATTTCCTT GTCICGAATT ATATGTGACA ATACCGGTAT CACCACGGTT TCAAGGGACA TCTTCAGAGC CAACATCTAC CCTC'GGGGCT TTGTGAACTG CAGCCGTATC CCCAGGTTGA ACCTATCAGC CTGGCGAGGG ACATGAGGCT TCTC'CAGGTA AGGGGAGGCC ACCTCCAGCA CCCTGGGCTG GTTAAGCCTC ACATCCTTCC CTGGATGGAT GGC GAGTCC TCTTAGGTCT CTAAGCAGAG AAAACAGAAC TTGTCACTAG GTACTCTTTC CAAGTGGCTT CCCAATGTGC TAGTTTCTGG GCTGACAGTC AATTCCAGGC CCTAGGACTT TGGGGGGAAA TTAGGAGCAT CCAACTA-3' (FRAG.NO: )(SEQ.ID NO:2489)

5'-GAATTCCGTG GCCAGGACCC CTGCCAGGGC ACTGACCCAG CCTCCCCTGG GGCAGTGGAG ACCTCGGTCC TGCGAGACTG CATAGCAGAG GCCAAGTTGC TGGTGGATGC TGCCTACAAT TGGACCCAGA AGAGCATCAA GCAGCGGCTT CGCAGCGGTT CAGCCAGCCC CATGGACCTC CTGTCCTACT TCAAACAACC GGTAGCAGCC ACCAGGACAG TTG TCGGGC CGCAGATTAT ATGCATGTGG CTTTGGGGCT GCTTGAAGAG AAGTTACAAC CCCAGCGGTC CGGACCCTTC ATTGTCACTG ATGTGCTAAC AGAACCACAG CTGCGGCTGC TGTCCCAGGC CAGTGGCTGT GCTCTCCGGG ACCAGGCCGA GCGCTGCAGC GACAAGTACC GCACCATCAC TGGACGGTGC AACAACAAGA GGAGACCCTT GCTAGGGGCC TCCAACCAGG CTCTGGCTCG CTGGCTGCCC GCCGAGTATG AGGATGGGCT GTCGCTCCCC TTCGGCTGGA CCCCCAGCAG GAGGCGCAAT GGCTTCCTTC TCCCTCTTGT CCGGGCTGTC TCCAACCAGA TTGTGCGCTT CCCCAATGAG AGACTGACCT CCGACCGTGG CCGAGCCCTC ATGTTCATGC AGTGGGCCA GTTCATTGAC CATGACCTGG ACTTCTCCCC GGAGTCCCCG GCCAGAGTGG CCTTCACTGC AGGCGTTGAC TGTGAGAGGA CCTGCGCCCA GCTGCCCCCC TGCTTTCCCA TCAAGATCCC ACCCAATGAC CCCCGCATCA AGAACCAGCG TGACTGCATC CCTTTCTTCC GCTCGGCACC CTCATGCCCC CAAAACAAGA ACAGAGTCCG CAACCAGATC AACGCGCTCA CCTCCTTTGT GGACGCCAGC ATGGTGTATG GCAGTGAGGT CTC/CTCTCG CTGCGGCTCC GCAACCGGAC CAACTACCTG GGGCTGCTGG CCATCAACCA GCGCTTTCAA GACAACGGCC GGGCCCTGCT GCCCTTCGAC AACCTGCACG ATGACCCCTG TCTCCTCACC AACCGCTCGG CGCGCATCCC CTGCTTCCTG GCAGGTGACA CCCGATCAAC GGAAACCCCC AAACTGGCAG CCATGCACAC CCTCTTTATG CGAGAGCACA ACCGGCTGGC CACCGAGCTG AGACGCCTGA ATCCCCGGTG GAATGGAGAC AAACTGTACA ATGAGGCTCG GAAGATCATG GGGGCCATGG TCCAGATCAT CACCTACCGA

GACTTTCTGC CCCTGGTTCT GGGCAAGGCC CGGGCCAGGA GAACCCTGGG GCACTACAGG GGGTACTGCT



CCAATGTGGA CCCACGGGTG GCCAATGTCT TCACCCTGGC CTTCCGCTTT GGCCACACAA TGCTCCAGCC CTTCATGTTC CGCITGGACA GTCAGTACCG GGCCTCCGCA CCCAACTCGC ATGTCCCACT TAGCTCTGCC TTCTTTGCCA GCTGGCGGAT CGTGTATGAA GGGGGCATCG ACCCCATCCT CCGGGGCCTC ATGGCCACCC CTGCCAAGCT GAACCGTCAG GATGCCATGT TAGTGGATGA GCTCCGGGAC CGGCTGTTTC GGCAAGTGAG GAGGATTGGG CTGGACCTGG CAGCTCTCAA CATGCAACGA AGCCGGGACC ACGGCCTTCC AGGGTACAAT GCTTGGAGGC GCT'CTGTGG GCTCTCCCAG CCCCGGAATT TGGCACAGCT TAGCCGGGTG CTGAAAAACC AGGACTTGGC AAGGAAGTTC CTGAATTTGT ATGGAACACC TGACAACATT GACATCTGGA TTGGGGCCAT CGCTGAGCCT CTT1TGCCGG GGGCTCGAGT GGGGCCTCTT CTGGCTTGTC TGTTCGAGAA CCAGTTCAGA AGAGCCGAGA CGGAGACAGG TTCTGGTGGC AGAACGAGGT GTTTTCACCA AAGACAGCGC AAGGCCCTGA 10 GCAGAATTTC CTTCTCGA ATTATATGTG ACAATACCGG TATCACCACG GTTTCAAGGG ACATCTTCAG AGCCAACATC TACCCTCGGG GCTTTGTGAA CTGCAGCCGT ATCCCCAGGT TGAACCTATC AGCCTGGCGA GGGACATGAG GCT CTGCAG GAGTCTATCC CAAGTCTCCA ACTTTTGGAG ACAAGGGGAA GGGGAGGACC ATGAGGCTGC CTTC/TCTCCC TGGAGCAGT GCAGGCTCGT GACGCTTCTG CTGGCTACAG CTCAGAGCTG GGTTCCCCAG CCAGGAGTGA AGGCTGGGGG CTCCTATCAG CAATGGACCT TCCGCCTTGG GAGCCTCTTA 15 GGTATTAGGC TATCAATCAG CGCCACGTGC AAAGGCTTGG GAGCCAAGCC ATGTGGTCTT GCACCCCAGG CAAGAAAAGT CAGCTGGAGG GTTTACAGCA CTTTCTACTG TTTCCCAGCC CTCCCTCCCC TCCCTCACCA TGACTAAGAG ACCACTCGGT CCTAGCCTCC AGACACCCCA CAATACTCCT CTGAGCCTGA GGCCAGGCAG CATGCTCTGC TTCTACCAAT AAAGCACTGC CGGAATTC-3' (FRAG.NO: ) (SEQ.ID no:2490) 5'-TC GGC CTG GTC CCG G-3' (FRAG. NO: 1727) (SEQ. ID NO:1740)

- 20 5'-TGG GGG TTT CCC; TTG-3' (FRAG. NO: 1728) (SEQ. ID NO: 1741)
  5'-TG GTC CCG GBG F.GC -3' (FRAG. NO: 1729) (SEQ. ID NO: 1742)
  5'-GCG CTC GGC CTG GTC CCG G-3' (FRAG. NO: 1053) (SEQ. ID NO: 1061)
  5'-GGG TCT CCT CTT GTT GC-3' (FRAG. NO: 1054) (SEQ. ID NO: 1062)
  5'- TTG CGC CTC CTG CTG GGG GT CC-3' (FRAG. NO: 1055) (SEQ. ID NO: 1063)
- 5'-CTC TGT TCT TGT 'ITT GGG GGC-3' (FRAG. NO:1056) (SEQ. ID NO:1064)
   5'-GGG CCC GGC CGT TGT CTT G-3' (FRAG. NO:1057) (SEQ. ID NO:1065)
   5'-GTT TGG GGG TTT CCG TTG-3' (FRAG. NO:1058) (SEQ. ID NO:1066)
   5'-GGG TTC TCC TGG CCC GGG CCT TGC CC-3' (FRAG. NO:1059)(SEQ. ID NO:1067)
   5'-GGC CGT GGT CCC GGC TTC GTT GC-3' (FRAG. NO:1060) (SEQ. ID NO:1068)
- 5'-CCT GTC TCC GTC ICG GCT CTT CTG-3' (FRAG. NO:1061) (SEQ. ID NO:1069)
  5'-GGG CCT TGC GCT GTC TTT GGT G-3' (FRAG. NO:1062) (SEQ. ID NO:1070)
  5'-GCB CCG TCC BGT GBT GGT GCG GTB CTT GTC GCT GCB GCG CTC GGC CTG GTC CCG GBG BGC -3' (FRAG. NO:1063) (SEQ. ID NO:1071)

## Human Intercellt lar Adhesion Molecule-1 (ICAM-1)

#### 35 Nucleic Acid and Antisense Oligonucleotide Fragments

- 40 TGC CBG GTC CTG GGB BCB GBG CCC CGB GCB GGB CCB GGB GTG CGG GCC GGG GCC GGG GGC TGC TGG GBG CCB TBG CGB GGC TGB G-3' (FRAG. NO: 1730) (SEQ. ID NO: 1743)
  - 5'-GGG GGC TGC TGG G-3' (FRAG. NO: 1731) (SEQ. ID NO:1744)
  - 5'-T GTC CTC CGG CCT CCC-3' (FRAG. NO:1732) (SEQ. ID NO:1745)
  - 5'-G CCB TBG CGB GC C TGB G-3' (FRAG. NO: 1733) (SEQ. ID NO: 1746)
- 45 5'-CTC TGG GGT GGC CTT C-3' (FRAG. NO:1734) (SEQ. ID NO:1747)
  - 5'-GCG CGG GCC GGG GGC TGC TGG G-3' (FRAG. NO:1064) (SEQ. ID NO:1072)
  - 5'-GGT TGG CCC GGG GTG CCC C-3' (FRAG. NO:1065) (SEQ. ID NO:1073)
  - 5'-GCC GCT GGG TGC CCT CGT CCT CTG CGG TC-3' (FRAG. NO:1066) (SEQ. ID NO:1074)
  - 5'-GTG TCT CCT GGC TCT GGT TCC CC-3' (FRAG. NO:1067) (SEQ. ID NO:1075)
- 5'-GCT GCG CCC GTT GTC CTC TGG GGT GGC CTT C-3' (FRAG. NO:1068) (SEQ. ID NO:1076)
  - 5'-GCT CCC GGG TCT GGT TCT TGT GT-3' (FRAG. NO:1069) (SEQ. ID NO:1077)
    5'-TGG GGG TCC CTT TTT GGG CCT GTT GT-3' (FRAG. NO:1070) (SEQ. ID NO:1078)
  - 5'-GGC GTG GCT TGT GTG TTC GGT TTC-3' (FRAG. NO:1071) (SEQ. ID NO:1079)
  - 5'-TGC CCT GTC CTC CGG CGT CCC-3' (FRAG. NO:1072) (SEQ. ID NO:1080)
- 55 5'- CGG BGC CTC CCC GGG GCB GGB TGB CTT TTG BGG GGG BCB CBG BTG TCT GGG CBT TGC CBG GTC CTG GGB BCB GBG CCC CGB GCB GGB CCB GGB GCG GGG GCC GGG GGC TGC TGG GBG CCB TBG CGB GGC TGB G-3' (FRA/3. NO:1073) (SEQ. ID NO:1081)

# Human Vascular Cell Adhesion Molecule 1 (VCAM-1)

#### Nucleic Acid and Oligonucleotide Fragments



5'-C TGT CGT-3' (FRAG. NO:1736) (SEQ. ID NO:<u>1749)</u>

5'-TGC TTC TTC C-3' (FRAG. NO:1737) (SEQ. ID NO:<u>1750)</u>

 ${\tt HSVCAM1AS1: 5'-CCT\ CTT\ TTC\ TGT\ TTT\ TCC\ C-3'\ (FRAG.\ NO:1074)\ \ (SEQ.\ ID\ NO:\underline{1082})}$ 

HSVCAM1AS2: 5'-CTC TGC CTT TGT TTG GGT TCG-3' (FRAG. NO:1075) (SEQ. ID NO:1083)

HSVCAM1AS3: 5'-CTT CCT TTC TGC TTC TTC C-3' (FRAG. NO:1076) (SEQ. ID NO:1084)

HSVCAM1AS4: 5'-CTG TGT CTC CTG TCT CCG CTT TTT TCT TC-3' (FRAG. NO:1077) (SEQ. ID NO:1085)

HSVCAM1AS5: 5'-GTC TTT GTT GTT TTC TCT TCC TTG-3' (FRAG. NO:1078) (SEQ. ID NO:1086)
CTG BGC BBG BTB TCT BGB TTC TGG GGT GGT CTC GBT TTT BBBB GCT TGB GBB GCT GCB BBC BTT BTC CBB
BGT BTB TTT GBG GCT CCB BGG BTC BCG BCC BTC TTC CCB GGC BTT TTB BGT TGC TGT CGT(FRAG.
NO:1079)(SEQ. ID NO:1087)

Human Endothelial Leukocyte Adhesion Molecule(ELAM-1) **Nucleic Acid and Antisense Oligonucleotide Fragments** 5'-BBG TGB GBG CTG BGB GBB BCT GTG BBG CBB TCB TGB CTT CBB GBG TTC TTT TCB CCC GTT CTT GGC TTC 20 GATACCCACC TGAGAGATCC TGTGTTTGAA CAACTGCTTC CCAAAACGGA AAGTATTTCA AGCCTAAACC TTTGGGTGAA AAGAACTCTT GAAGTCATGA TTGCTTCACA GTTTCTCTCA GCTCTCACTT TGGTGCTTCT CATTAAAGAG AGTGGAGCCT GGTCTTACAA CACCTCCACG GAAGCTATGA CTTATGATGA GGCCAGTGCT TATTGTCAGC AAACGTACAC ACACCTGGTT GCAATTCAAA ACAAAGAAGA GATTGAGTAC CTAAACTCCA TATTGAGCTA TTCACCAAGT TATTACTGGA TTGGAATCAG AAAAGTCAAC AATGTGTGGG TCTGGGTAGG AACCCAGAAA CCTCTGACAG AAGAAGCCAA GAACTGGGCT CCAGGTGAAC CCAACAATAG GCAAAAAGAT GAGGACTGCG TGGAGATCTA CATCAAGAGA GAAAAAGATG TGGGCATGTG GAATGATGAG AGGTGCAGCA AGAAGAAGCT TGCCCTATGC TACACAGCTG CCTGTACCAA TACATCCTGC AGTGGCCACG GTGAATGTGT AGAGACCATC AATAATTACA CTTGCAAGTG TGACCCTGGC TTCAGTGGAC TCAAGTGTGA GCAAATTGTG AACTGTACAG CCCTGGAATC CCCTGAGCAT GGAAGCCTGG TTTGCAGTCA CCCACTGGGA AACTTCAGCT ACAATTCTTC CTGCTCTATC AGCTGTGATA GGGGTTACCT GCCAAGCAGC ATGGAGACCA TGCAGTGTAT GTCCTCTGGA GAATGGAGTG CTCCTATTCC AGCCTGCAAT GTGGTTGAGT GTGATGCTGT GACAAATCCA GCCAATGGGT TCGTGGAATG TTTCCAAAAC CCTGGAAGCT TCCCATGGAA CACAACCTGT ACATTTGACT GTGAAGAAGG ATTIGAACTA ATGGGAGCCC AGAGCCTTCA GTGTACCTCA TCTGGGAATT GGGACAACGA GAAGCCAACG TGTAAAGCTG TGACATGCAG GGCCGTCCGC CAGCCTCAGA ATGGCTCTGT GAGGTGCAGC CATTCCCCTG CTGCAGAGTT CACCTTCAAA TCATCCTGCA ACTTCACCTG TGAGGAAGGC TTCATGTTGC AGGGACCAGC CCAGGTTGAA TGCACCACTC AAGGGCAGTG GACACAGCAA ATCCCAGTTT GTGAAGCTTT CCAGTGCACA GCC TGTCCA ACCCCGAGCG AGGCTACATG AATTGTCTTC CTAGTGCTTC TGGCAGTTTC CGTTATGGGT CCACCTGTGA GTTCTCCTGT GAGCAGGGTT TTGTGTTGAA GGGATCCAAA AGGCTCCAAT GTGGCCCCAC AGGGGAGTGG GACAACGAGA AGCCCACATG TGAAGCTGTG AGATGCGATG CTGTCCACCA GCCCCCGAAG GGT TGGTGA GGTGTGCTCA TTCCCCTATT GGAGAATTCA CCTACAAGTC CTCTTGTGCC TTCAGCTGTG AGGA.GGGATT TGAATTATAT GGATCAACTC AACTTGAGTG CACATCTCAG GGACAATGGA CAGAAGAGT TCC1TCCTGC CAAGTGGTAA AATGTTCAAG CCTGGCAGTT CCGGGAAAGA TCAACATGAG CTGCAGTGGG GAGCCCGTGT TTGGCACTGT GTGCAAGTTC GCCTGTCCTG AAGGATGGAC GCTCAATGGC TCTGCAGCTC GGACATGTGG AGCCACAGGA CACTGGTCTG GCCTGCTACC TACCTGTGAA GCTCCCACTG 45 AGTCCAACAT TCCCTTGGTA GCTGGACTTT CTGCTGCTGG ACTCTCCCTC CTGACATTAG CACCATTTCT CCTCTGGCTT CGGAAATGCT TACGGAAAGC AAAGAAATTT GTTCCTGCCA GCAGCTGCCA AAGCCTTGAA TCAGACGGAA GCTACCAAAA GCCTTCTTAC ATCCTTTAAG TTCAAAAGAA TCAGAAACAG GTGCATCTGG GGAACTAGAG GGA'TACACTG AAGTTAACAG AGACAGATAA CTCTCCTCGG GTCTCTGGCC CTTCTTGCCT ACTATGCCAG ATGC:CTTTAT GGCTGAAACC GCAACACCCA TCACCACTTC AATAGATCAA AGTCCAGCAG GCAAGGACGG CCT CAACTG AAAAGACTCA GTGTTCCCTT TCCTACTCTC AGGATCAAGA AAGTGTTGGC TAATGAAGGG AAAGGATATT TTCTTCCAAG CAAAGGTGAA GAGACCAAGA CTCTGAAATC TCAGAATTCC TTTTCTAACT CTCCCTTGCT CGCTGTAAAA TCTTGGCACA GAAACACAAT ATTTTGTGGC TTTCTTTCTT TTGCCCTTCA CAGIGTTTCG ACAGCTGATT ACACAGTTGC TGTCATAAGA ATGAATAATA ATTATCCAGA GTTTAGAGGA AAAAAATGAC TAAAAATATT ATAACTTAAA AAAATGACAG ATGTTGAATG CCCACAGGCA AATGCATGGA GGGTTGTTAA TGGTGCAAAT CCTACTGAAT GCTCTGTGCG AGGGTTACTA TGCACAATTT AATCACTTTC ATCCCTATGG GATTCAGTGC TTCTTAAAGA GTTCTTAAGG ATTGTGATAT TTTTACTTGC ATTGAATATA TTATAATCTT CCATACTTCT TCATTCAATA CAAGTGTGGT AGGGACTTAA AAAACTTGTA AATGCTGTCA ACTATGATAT GGTAAAAGTT ACTTATTCTA GATTACCCCC TCATTGTTTA TTAACAAATT ATGTTACATC TGTTTTAAAT TTATTTCAAA AAGGGAAACT ATTGTCCCCT AGCAAGGCAT GATGTTAACC AGAATAAAGT TCTGAGTGTT TTTACTACAG TTGTTTTTTG AAAACATGGT AGAATTGGAG AGTAAAAACT

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					TGGGAAATAA		
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					TAAAGATACA		
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					TTGATATATA		
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	AGTCATGAGA	TAA' GATTTA	CATGGTCATT	GTTAGTAAGC	TAATAGCTAA	GTGCATGAAC	TCTGGAGCTA



	GCCTCCCTGG	ATTITAATCC	CAGATCTGTC	ACTGACCAGC	TGAGCAATAC	TAGGTAAATT	GCTCTTGTTC
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	TACGCTTATC	ATCA.CTTATA	CTAGCATACC	CTGTTGTGCA	AATGCTGTCT	GTGTTTGCAT	CTGCTATTGT
	TGATGCCTGG	TGCATGAATC	AGGACTCCAG	CCCACAAGTT	TTCCCAGAAC	TTTCTTATGG	CCATCATCTT
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	CAGTCGTTAC	ATTTCAATAG	AGCAGGAAGG	GGAAATGGTG	GCCTGTAACC	TCAGGGAATT	TTGCCAGTTG
	GTCCACCCCA		CCTGCTCTGA		CAGCCTAGAA	CAGCACCACA	GGTGAGAGAA
	ATGCAAACCC		AGCAGACTCT	TTGCCAGTAG	TAATAGTTCA	GGACCACCAC	CAGCTTTTAT
	TAAAATTTTT	AATAACACTC	AAGTATTGGC	AGAAAGAAAT	AATCTTGGGT	TAACTATAAC	TAGAATATTG
25	ACTCTTCCTC	TGTGGAAGAA	TCAGCCAATC	ACATTTGTTT	ACATCAGTTC	CCCTGAAGAA	GAAAAATACA
20	CTGATGTTGC	AGCA AGACAA	ATTTAAGCTA	GATGTAAATA		GCCTGTAATG	CTAGGCTAAT
	TACATATTGG	AACTATTTT		ATTGTGTAGG	GTTTCAGGGA	AGAATTCTGA	AGAAAATATA
	GAGCTGAAAT	GATCTTGCAG	CTCACTGAAA	CTGCAGGGTT	TAGATCCACA	CTGATACTCG	TTCTATTATC
	ACTGTAATGA	AGGCTGATGG	AATAAGTAAA	AATGTTTTGT	ATTAGTATGT	TTTTACACTT	ATTTGCAAGG
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	GGGTGGCTCA	CGCCTGTAAT		TGGGAGGCCA		ATCAAGAGGT	CAGGAGATGG
	AGACCATCCT	GGCTAACACG	GTGAAACCCC	GTCTGTACTA		AAAAAAAAA	AGCCAGGCGT
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	AAAAAAAAA			CAGAGGGGTA		CTGGGCTGTC	AGTCAACTCA
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	TAATCCTCAC				CCACTTTACA		CTGAGGGTTA
60					AGATACAAAT		
• •	ACTAGATATT	TAAC CATTTT	AATTCAAGCT	TTAAAACTGC	TAAATAAAAT		
					AATCTTTGAT		
		J. L. COLIMITO		COMMITTINGA	MICHIGAL	GCITCAGAGI	CONCACIONA



	ATGTGGAGGC	ACA'TAGTGAG	TTGGTCCCCA	GCCTTCAGTC	CACCCACCTT	CTCTTTACTA	AATCACCTTT
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	TTATTATTTG	CCACTCACTG	TTCTAAATTC	TTTACATGTA	TTATACAACT	GCCATATAAC	TGCCATATGA
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	CTGGTACATT	GAGACAGGGT	CGGCCAGTCT	GCGTTAGGGT	CTTGGTCAAA	ACTGCATTTC	TGAAACTAAA
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				ATTCAAAAGC			
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	ССССТСТСАТ	CCTC CTCTTT	CCTCCATCAC	A A A C A TO CO A C	OT A TO A COMO	TO CT COT CA C	1001100100
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	COLLOCATE	TO A COTTO A A M	mamamam am	A TOTAL COMPO	1 COTTO CA LO LA	mmmm A A CM CM	mmma + mmmma
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	C.L.L.CCLTTCC	4 C 4 2 TO COTTO	maan				
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	TGCCAAAAAT	AGAAAACAGC		TTGAAAATGT	CTAACTTTAA		GTGTGTCACT
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	GCACTCCCTA	CCCC CAAGCA	CAGATAGCCT	CCCCCAGTAT	CAGCATCCCG	CACCAGAGTG	GTACATTTAT
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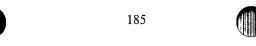
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	TGCTTCCCGA		GATCGCGCTT	CTGAAAAAGC		ACGCCTCCTC	CGGACCTAAA
					CCCGACTTTC		TGAGGGACCC
						GGAGAGCGCG	
15						TCCTGTTTGA	
45						TAGCTGGCCA	
						GGTTGTCACT	
						CCGCCAGGCT	
						GAGGGACTGG	
60						CGTGTTCTGA	
50						CTCGTTGCTT	
						GGTATGACGA	
						AAAAGGGTGG	
						GAAATCTTTA	
					CTTTTTCTTC		TTTTTTTGAC
55					AGAGTTCTTC		
					GCAGCACATT		
					AAACCATATG		TTTTTCACAA
						TCACTTGAGA	
						TTCACCTAGG	
60						ACTGCCGTCT	
						TGCGTGCATA	
	GACATGGTGT	TAGGCTTTGG	GAGAACAGAG	ACACGGAACG	TGATTCCTCT	TCTTCCCCAC	AAGCTTATAG



	10101000000	mm + + 0 mm C + +	. cmc c. mm	aaa, aan, aa			
	AGAGACTTCA	TTAAGTTGAA		CCCACCTAGC		AAACGACATA	TTCAAAAAAG
	CCCAAACTTC	CTCTAGTTTT	CTTCATCTGA	GTAAATGGTT	TCACAAACTG	AAACCTTGAA	TCCTCTCTGT
	CTCACACACC	CGATCAGTAA	GTTCTATTGT	TTCTGATTCC	AAACTATGTC	TTGAATCAAT	CCGTTTATCT
5	CCATCCTCAT	TGCTACCACT	CTGATTCCAA	ACCCTTATCA	CCTCTCACTT	GGAGTATTAA	TAGTTTCCTT
J	GTTTCTACTC TTAAACCACT	ATAA FTCATT TTACCTTCAA	ATTCCAAAAA	AGTTAAGAGG	GGAAAAACAT	AGATCTCGTC	ATTTCCCTTT
	TACACTCTGT	TCATGAATAC	GGTTCCAGGT ATTAGGCTCA	GATCTAAGCC	TTGCCCTTCT	CTCACACCTCA	GTTAATTAAC
	CAGCCTTTTG	CATATTTCAT	GTTTATGTCT	CCTACCTCAA TGGCCCAAAT	GATCTTTTTG GTCACTTCCT	CTCAGCCTGA TAGAGGGGCT	TTTGTTCTCT TTTTCAGAGC
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10	AAAGCACATT	ACCATTAAAA	GAAATGCTCT	TGTTTGCTTT	GTATATTTTC	CACTTCTACA	CATTATGTTG
10	CAAAGTTCAT	AAACGCAGGA	TGTTGATTTT	CTTCACAGCG	TTACCCTCAG	CACCTAGAAC	AGTGCCTGAC
	ACATAGTAAG	CATICATTAA	AGGGCTAAAA	ATATTTCATG	TTTTAAAAAT	ACTTGGGAGT	CTAATTAGAC
	AATACTTTTT	TTCA GCTTAA	TGGTAGTATT	TTAGCTTCAC	TATTTTAACA	AATGAAAAAT	TTGCAATAAA
	TCTACAATGC	CATTACCCCC	CAAAATCTTT	TTCATGTTTT	GCATTTTACG	TATTATTTTC	CAGGCCTTAC
15	CTGCATGTCT	GCATAATCAT	AACTGACTAA	TTTTGGAACA	GCTGGTAATT	ATTTGAGCTT	TACTGAAATT
	TTTTCATGAG	GCCAATTCTA	CCCTACTGAA	CTCAAATTTG	AGTTAATGAT	GACCTCATTT	TGATTGCTGC
	TGTAAAAAAT	AAGATTTCGG	AAGAGGAATG	AATTCTTGTA	TTACTGTGGT	AGGACTATGG	GTTTTTTTT
	GTTTGTTTGT	TTGT TTGAG	ACGGAGTCTC	ACCCTGTCAC	CCAGGCTGGA	GTGCAGTGGT	GCGATCTCAG
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	ACTCCTGACC	TCGTGATCCG	CCTGCCTCAG	CCTCCCAAAG	TGCTGGGACT	ACAGGCGTGA	GCCACCGTGC
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25	AGAAGGTGAT	GAG1'GACTTA	GGTATAAATT	AAGTACAATA	GAAATGTTGA	GGAAAGAAAA	
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	GGGTGACAGC	AAGACCGTCT	CTCTTTTTT	TTTTTTTTGA	GACGGAGTCT	CGCCTATGCT	GGAGTGCAAT
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	GAAAATGCTT					TTACCATTTG	
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		GTGCTGCGAA				CACGCTCAAG	
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<i>E E</i>	CCTTAACCTA		TTTAGTTACT	GTAATTTCTC			
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	CTCCTGACCT	CAGCITAATCC	ACCTGCCTCA	GCCTCCCAAA	GTGCTGGGAT		AGCCACCGTG
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	AGGCGTGAGC	CACCGCGCCC	GGCCTGCCCC	CAATTATTTA	GTTTTTCTAT	AAACAGGGAA	ATTTATTTGT
	GTGGCCCTTA	GAACTAATTT	AATTTCCACT	CTAATTCCTA	CTTATGTTTA	TATAATGCTT	TTAGAAATTT
	GTATTATTCA	GAA/ATAAAC	ATATACTATT	GTATCTGTTG	CCTACACTTA	GATTTTATTG	CCTGCTATAT
	TTAAATTTTA	TTAGTATTTT	AATTGTTTTA	TTAAAGAAAG	AATGTGCCTG	TAATCTCAGC	ACTTTTGAGA
30		GAAGGATTGC			CCAGACTGAG	CAACACAGGG	AGACCCCCAT
		AATA.AAAAAA			ATACCTGTAG	TTCTAGTTAC	TTGGGAGACT
				TTGAGGCTGC		GATCAGGCCA	CTGTACTCCA
		CAGA.GTGAGA			AGATAGATAA	TCTAAATAGA	TAATAGACAG
	ATTATCTAAA	TAGATAATAG		TAAATAGATA	ATAGACAGAT	TATCTAAATA	GATAATAGAC
35	AGATTATCTA	AATA GATAAT		TCTAAATAGA	TAATAGACAG	ATTATCTATC	TAAATAGATA
	ATAGATTATC		ATAGATAGAT		GATAGATAGA	TAGATAGAGC	TTGGACAACA
	GAGTGAGAGC			AAAGAAAGAA			TTTAAAGCAT
	TGAAAAATGG	TCT CCTTGC	TTATATTACC	CACACCTTCT	TTGTTGGCAT	TAAGATGCAA	ACTTTGTTTT
	AAACAGTTGA	GTAAATCAAA				ACCTGCTTTT	TGAAAATGTA
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	ATCTTGTGTA		GAATGAGAGA	GAAAATTTAA	AGTAAGCAAA	CAAATAAGTT	GTGTGTCACC
	ACTCATTCAG		AGTATTTCCA	GAGTACTTAT	TCTGTGCCAG	GAAATGTTGT	AGGTGCCCTC
					ATTATTATAG		
					CCAGTGATGA		
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15					GGCTGAGTGT		
					TAGGAGTTCG		
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					GGTGGAGGTT		
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50					ATTTTCAAAT		
					TCCTTTTGGC		TGGATGTGTA
					ATCATGTGGA		
					TAATTTGGTC		
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					AGACCTTATC		
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					CCGTCCTCAA		
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00					CCTGAAGCGA		
					ATGCCACATC		
	IIIOAAIAIA	JUJUTTUUACA	UCATAAAACC	IOIAIUCICA	AIGCCACAIC	AAAATICAIG	3/1011CIACC



AAGATGTAAA GGACTGGTGG CTCTTCGGGT TCTATTTCTG TATGCCCTTG GTGTGCACTG CGATCTTCTA CACCCTCATG ACTGGTGAGA TGTTGAACAG AAGGAATGGC AGCTTGAGAA TTGCCCTCAG TGAACATCTT AAGCAGCGTC GAGAAGTGGC AAAAACAGTT TTCTGCTTGG TTGTAATTTT TGCTCTTTGC TGGTTCCCTC TTCATTTAAG CCGT TATTG AAGAAAACTG TGTATAACGA GATGGACAAG AACCGATGTG AATTACTTAG TTTCTTACTG CTCA'TGGATT ACATCGGTAT TAACTTGGCA ACCATGAATT CATGTATAAA CCCCATAGCT CTGTATTTTG TGAGCAAGAA ATTTAAAAAT TGTTTCCAGT CATGCCTCTG CTGCTGCTG TACCAGTCCA AAAGTCTGAT GACCTCGGTC CCCATGAACG GAACAAGCAT CCAGTGGAAG AACCACGATC AAAACAACCA CAACACAGAC CGGAGCAGCC ATAAGGACAG CATGAACTGA CCACCCTTAG AAGCACTCCT-3' (FRAG. NO: 1738) (SEQ. ID NO: 3009) 5'-GCCACCATGG AAACCCTTTG CCTCAGGGCA TCCTTTTGGC TGGCACTGGT TGGATGTGTA ATCAGTGATA ATCCTGAGAG ATACAGCACA AATCTAAGCA ATCATGTGGA TGATTTCACC ACTTTTCGTG GCACAGAGCT CAGCTTCCTG GTTACCACTC ATCAACCCAC TAATTTGGTC CTACCCAGCA ATGGCTCAAT GCACAACTAT TGCCCACAGC AGA(TAAAAT TACTTCAGCT TTCAAATACA TTAACACTGT GATATCTTGT ACTATTTTCA TCGTGGGAAT GGTGGGGAAT GCAACTCTGC TCAGGATCAT TTACCAGAAC AAATGTATGA GGAATGGCCC CAACGCGCTG ATACCCAGTC TTGCCCTTGG AGACCTTATC TATGTGGTCA TTGATCTCCC TATCAATGTA
TTTAAGCTGC TGGCTGGGCG CTGGCCTTTT GATCACAATG ACTTTGGCGT ATTTCTTTGC AAGCTGTTCC CCTTTTTGCA GAAGICCTCG GTGGGGATCA CCGTCCTCAA CCTCTGCGCT CTTAGTGTTG ACAGGTACAG AGCAGTTGCC TCCTGGAGTC GTGTTCAGGG AATTGGGATT CCTTTGGTAA CTGCCATTGA AATTGCCTCC ATCTGGATCC TGTCCTTTAT CCTGGCCATT CCTGAAGCGA TTGGCTTCGT CATGGTACCC TTTGAATATA GGGGTGGACA GCATAAAACC TGTATGCTCA ATGCCACATC AAAATTCATG GAGTTCTACC AAGATGTAAA GGACTGGTGG CTCTTCGGGT TCTATTTCTG TATGCCCTTG GTGTGCACTG CGATCTTCTA CACCCTCATG ACTGGTGAGA TGTTGAACAG AAGGAATGGC AGCTTGAGAA TTGCCCTCAG TGAACATCTT AAGCAGCGTC GAGAAGTGGC AAAAACAGTT TTCTGCTTGG TTGTAATTTT TGCTCTTTGC TGGTTCCCTC TTCATTTAAG CCGTATATTG AAGAAAACTG TGTATAACGA GATGGACAAG AACCGATGTG AATTACTTAG TTTCTTACTG CTCATGGATT ACATCGGTAT TAACTTGGCA ACCATGAATT CATGTATAAAA CCCCATAGCT CTGTATTTTG TGAGCAAGAA ATTIAAAAAT TGTTTCCAGT CATGCCTCTG CTGCTGCTGT TACCAGTCCA AAAGTCTGAT GACCTCGGTC CCCA'FGAACG GAACAAGCAT CCAGTGGAAG AACCACGATC AAAACAACCA CAACACAGAC CGGAGCAGCC ATAACGACAG CATGAACTGA CCACCCTTAG AAGCACTCCT-3'(FRAG.NO: )(SEQ. ID NO: 2481) 5'-GATCAAAATT TTIACCTATT ATGCATTTGA TATATAAATA AGTATATAAA TGCACACACA GACACAGCAA TGATGGTGAA CAGTCTTCAT ACAATTATAT GGATGAATCT CATAAAATGC TGAGTTAAAG AAATCAGACC AAAGAACATA TACIGAAAGA TTCTCTCTAT ATACAAAGTT CAAAAAATAGG TGGACCAATT CATGGTGGTG
TTAGAAATCA GAAGAGGC TACCTTTGTG GGGAGGGGAC AGTTTAATGC CCAGAAGCGG TAAATAAGGA
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GAGACTTTC TGTCTGTTAC TGTTTCTTCA TTCCTCATCT GCAGAGCCAG CCCTGAGAAG TGCAGACCAA
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CATCAGTGGT AGACTAGCTA AAAAAAAAAA AATGTGGTAC ATATACATCA CAGAATAGTA TGCAGCCATA AAAATGAACA AGAI'CATCAT GTCCTTTGCA GCAACATGGA TGTAGTTGGA GGCCATTATC CTAAGCAAAT TAATGCAGGA ACACAAAGCC AAATACCACA TGTTCTCATT TATAAGTGAC AGCTAAATAT TGAGTACACA TGGACACAAA GAAGGAACA ATAGACATGG GACCTACTTG AGAATAGAGG GTGGGAGGAG GGTGAGGATC AAAAAGTACC CATAGGACAC TGTGCTTATT ACCTGGGTGA TGAAATAATT TGCACACCAA ACCCCTGTGA CACACAATTT ACCTATATAG AAAACCTGTG CATGTACCCC TGAACCTAAA AGTTAATGGT GGGGGGGTGG GGTTAAGCTA CTTT FTGGTA TAAATCTGAG CATTCATATT AAAATAAAAT ATTTACCTCA TTAGAGTAAT

TAACATTTAT TAAGCAAAGA GCCAAGTACC TTACACACAT GATGTTTAAT CTCACAATGA TCTTTAATCT



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_	AGCAAATATT	TATTTAAATA	TTCAAGATAT	GCTGTTAAAT		AAATTTGAGT	ACAGTATGGA
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	CTTTAACATC	TTGCCTTTAC	TTTATAACAT	TTATCACAGC	AGTCATGAGA		CATGGTCATT
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	AGCCGCATGC	ATGC AAGGAC			TTGCATCCCC		ACAGTGTGCA
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	AGGCCACTGC				GCAGAATACA		TGTCCCTGGA
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	GTTTAAGCAT	TTTAAATGCC			CACAACAAAT	ACCCAGTGAG	AGAGGGAGAA
	GGGAAGTAAA			AATGTCAGTA			ATGAACAATA
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		CAAACGATTC				TGGAAGGTAC	TCCTTTTTAG
		CCCCTCTTCT		AAGTTTTTTC	TTTCCATTTT	AAAAATCGTG	AATTCCTTTT
	TGCAATATTG	AGG1GGTTAT	ATGGTTTCTC		TGTTAATATG	GTGATTTAAT	
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	AGCTATGTGA	CTTTTGAACT	TATGAGTTAT	TTAAATATTT	TTAAATTATT	AAGCATATTG	GGATTTTAAG
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					511.11.001.01		



TTTATTGACA TTTGTTCAT AGTCTATTAT ATGGTCTACT TTTGTTCATG TTACATCTGT AGTAGAATTG GCTAATAGTT GAGTAAAGTA CACATATGTC TATGAAATCA AGTGTAATCC AGAGAAAAAG AGAAATTTAC TGAATATATT GTTCIAGGTG CTATTATATG TTGTCATGTT TAATCCTCAC CACAATTGTA TGAGGCAGCC ATAATTAATT CCACITTACA CATGAGGAGC CTGAGGGTTA AAAAAAAAGC TAGCTCTACT ATTTGTAAAG AATGAAGCAA AGATACAAAT GAAGGCCCAC ATATCCTATA ACTAGATATT TAAGCATTTT AATTCAAGCT TTAAAACTGC TAAATAAAAT GTGCTCCAAT TTCTATATTG ACAGACATAC CTTCCTAATG AGCTGGGGTT CGAATTTAGA AATCTTTGAT GCTTCAGAGT CCACACTGAA ATGTGGAGGC ACATAGTGAG TTGGTCCCCA AGTCCAAACC CTAAACAAAA TGGGACACCC TTGTGCATAC ACAGAGACAC AGCCCATCCT CAGGAAAACC TGGAAAAGTC CATACAAGTT CTGGAAGCAA GCTTGGGACG GTTTCAGTAG TGTGGTCTAT AAGGGAGGCC TCAGAAGACA GGTTTCTTA ATTCTGTGAA CTTCTCCCAC AGTAGAAAGG GTGCTGGAGG AGGGTCAGAG TGAGGACTTC TAAAGCATGG GTCCTGAGTA GGGGCCACTC TTGCCCAAGT CTAAGAAGGG TACTAGAATA GCACACTACT ACTAGATACT AGAACCCAGA TACAAGCACA GGTCTTCTGA AATTAATAAT AATAATAACT ATTACCATTA TTATACCAGT AGCTGTCATT TATTTAGTGC TTATTATTTG CCAGTCACTG TTCTAAATTC
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	GCCGTAACTC	AGATCGGGGA	ACCTCCCTTG	GGAGATCAGT	CCCCTGTCAT	CCTGCTCTTT	GCTCCATGAG
	AAAGATCCAC	CTATGACCTC	TGGTCCTCAG	ACCAACCAGC	CCAAGGAACA	TCTCACCAAT	TTTAAATTGG
	GTAAGTGGCC	TCTTTTTACT	CTCTTCTCCA	GCCTCTCTCA	CTATCCCTCA	ACATCTTTCT	CCTTTCAATC
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5	AACGTGTTCT	ATCT 3TGAAC	CCAAAACTCC	AGCACTGGTC	ATGGACTTGG	AAAGACAGTC	TTCCCTTGAT
	GTTTAATCAC	TGCAGGGATG	CCTGCCTGAT	TATTCACCCA	CATTTCAGAG	CTGTCTGATC	ACTGCAGGGA
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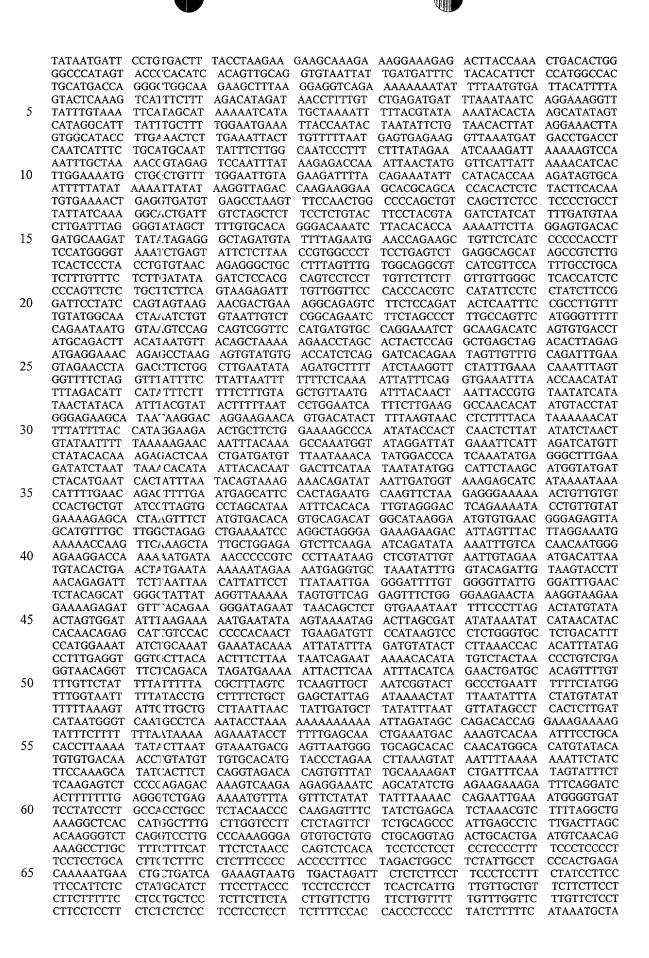
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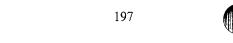


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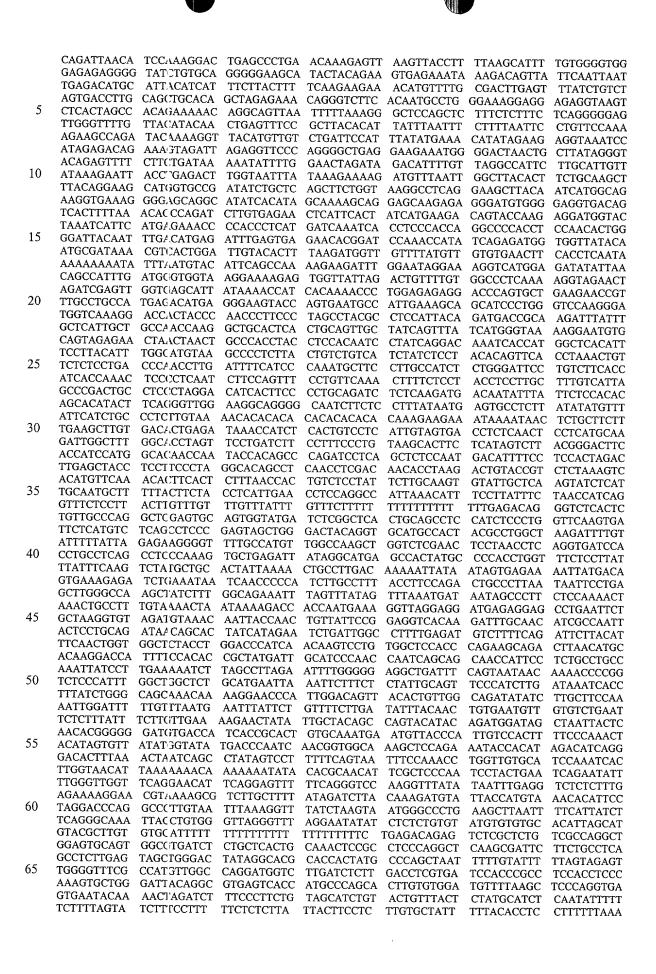


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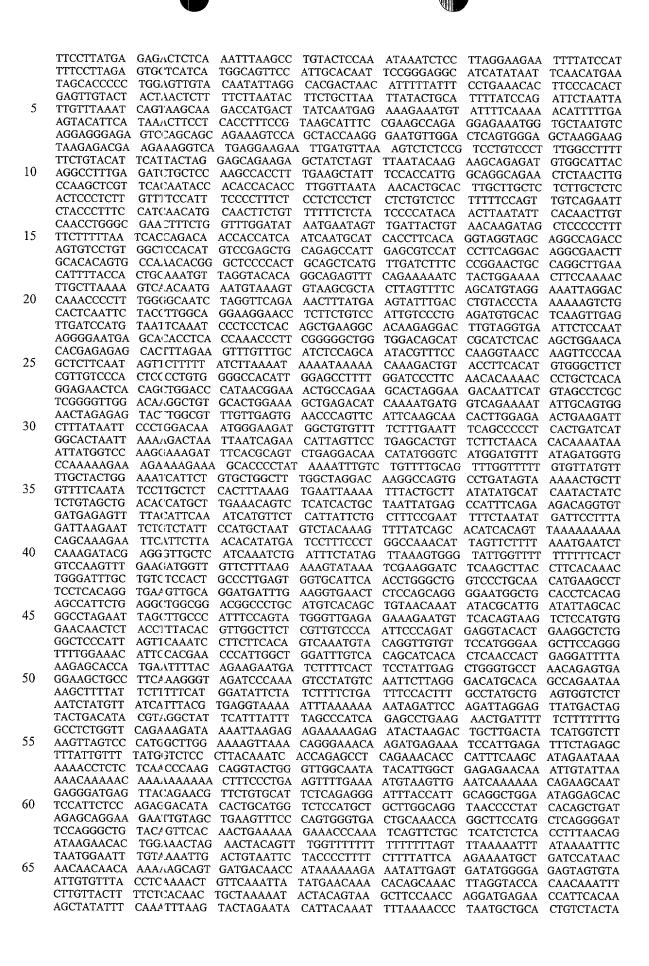


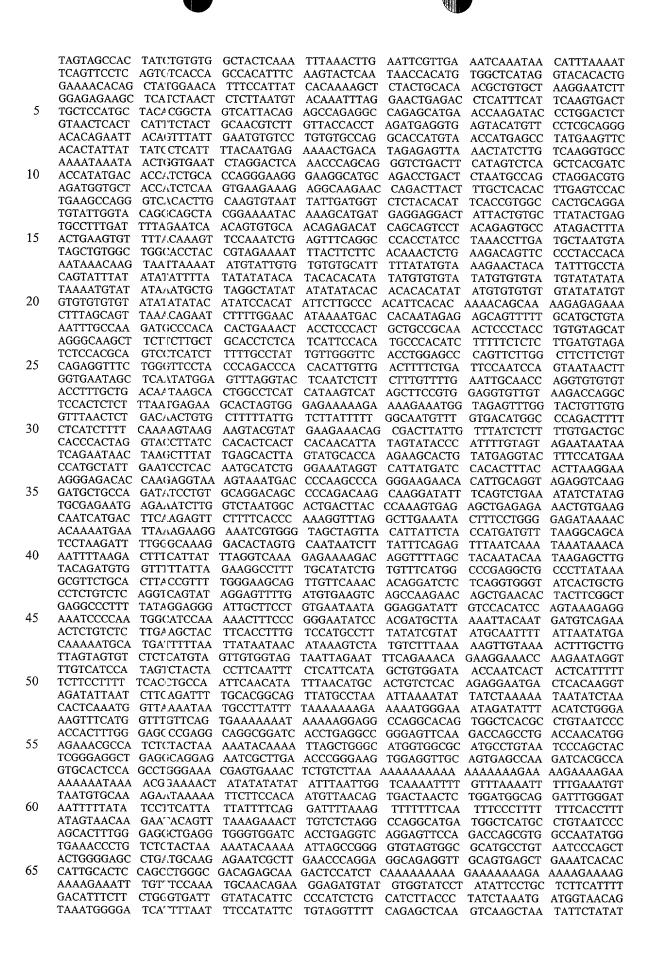
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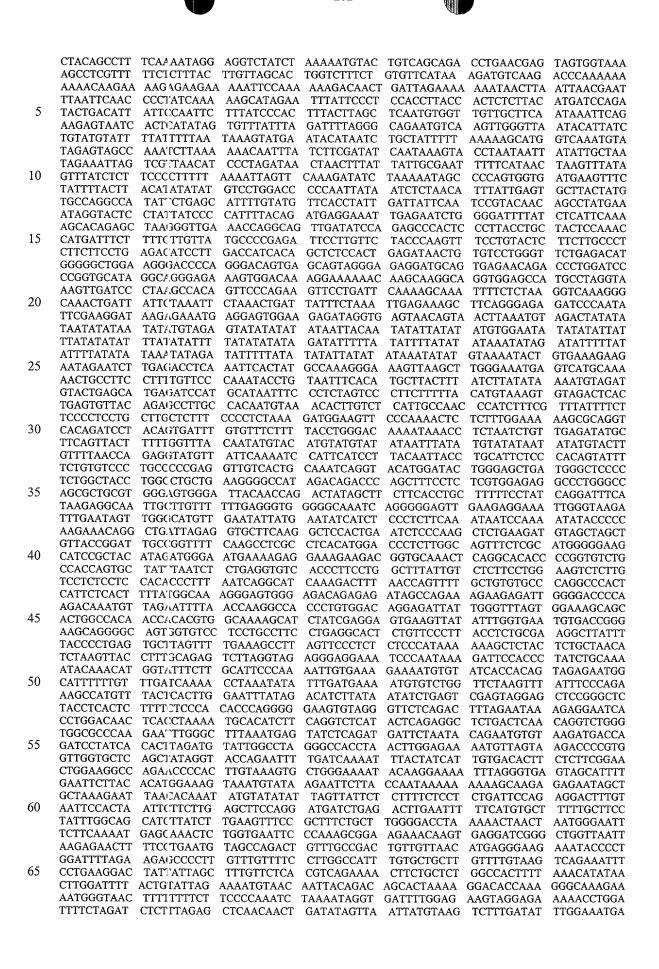


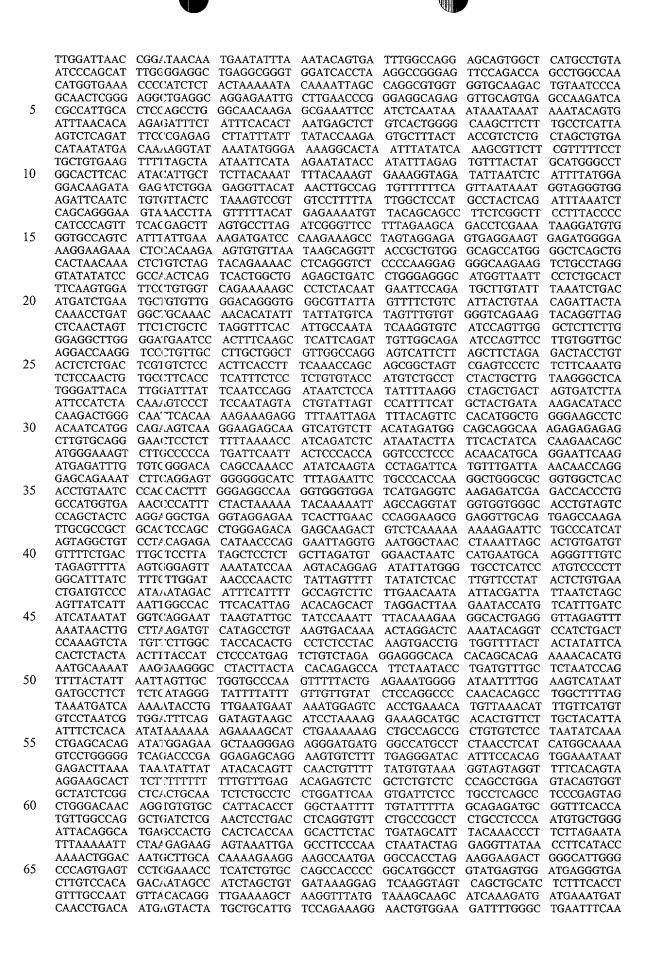


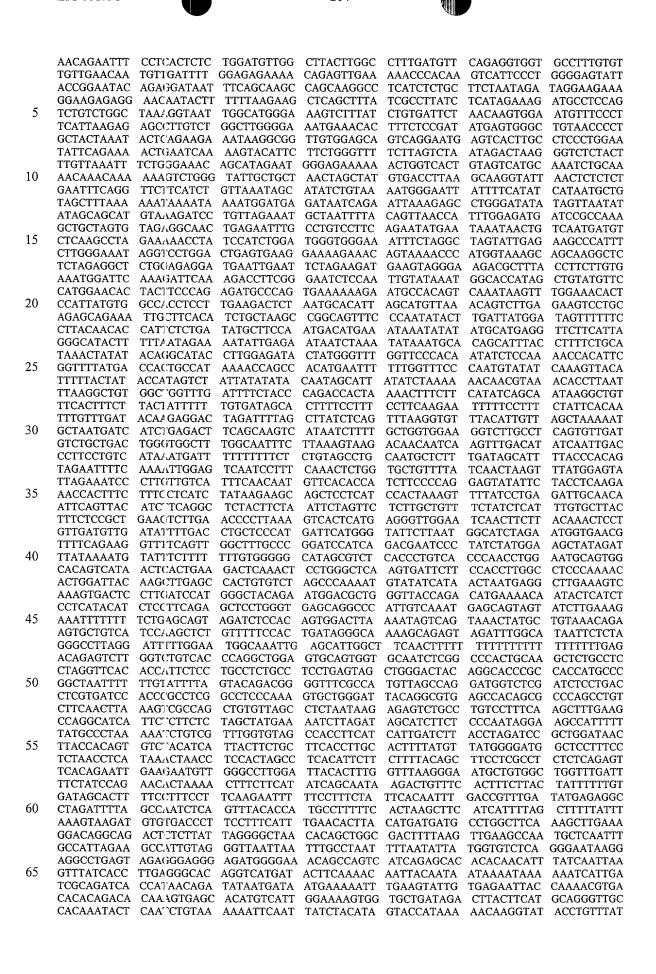
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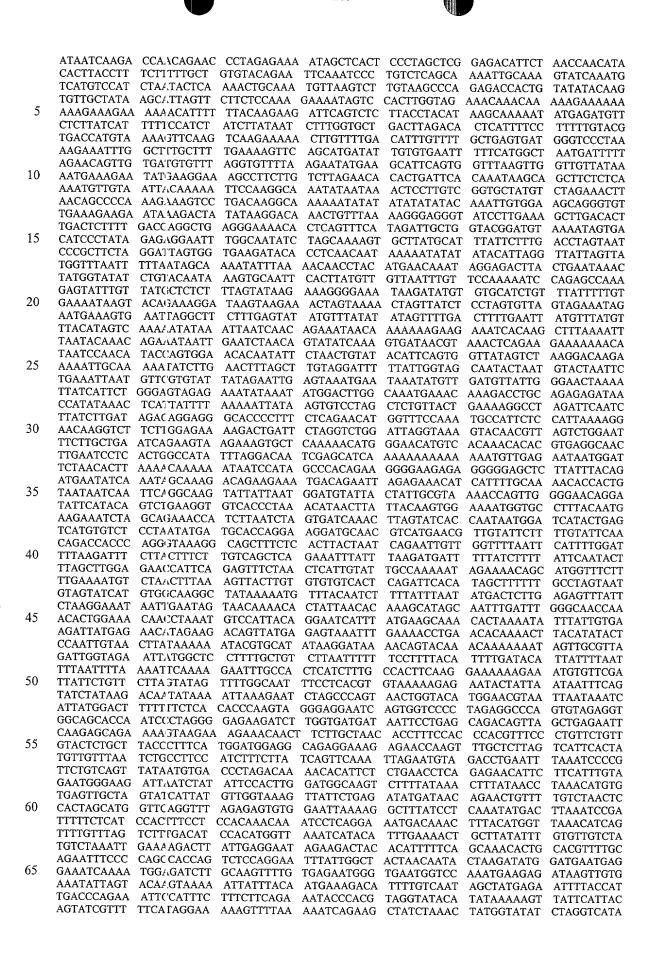


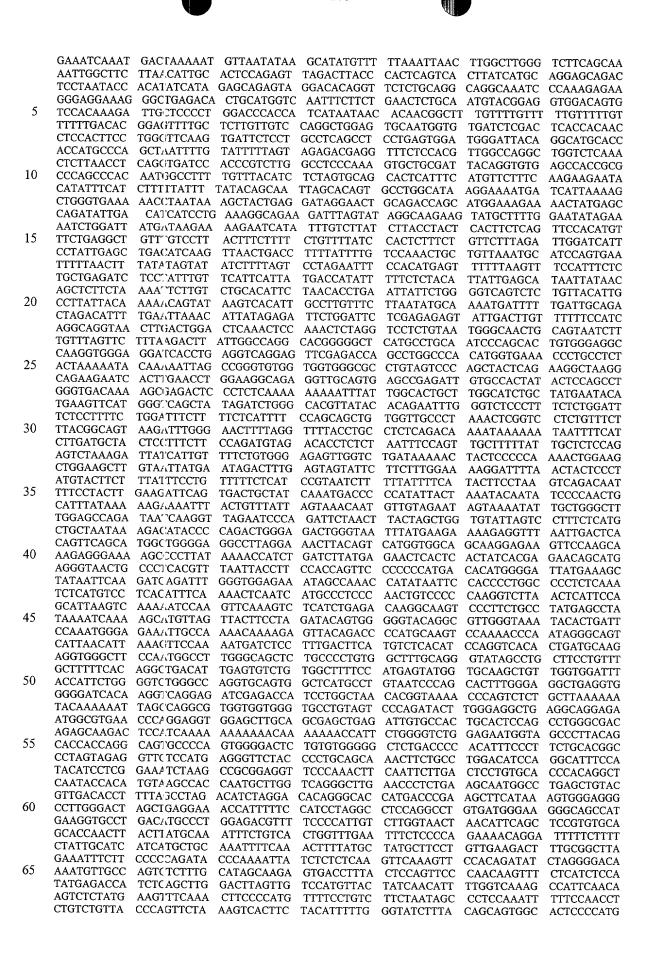


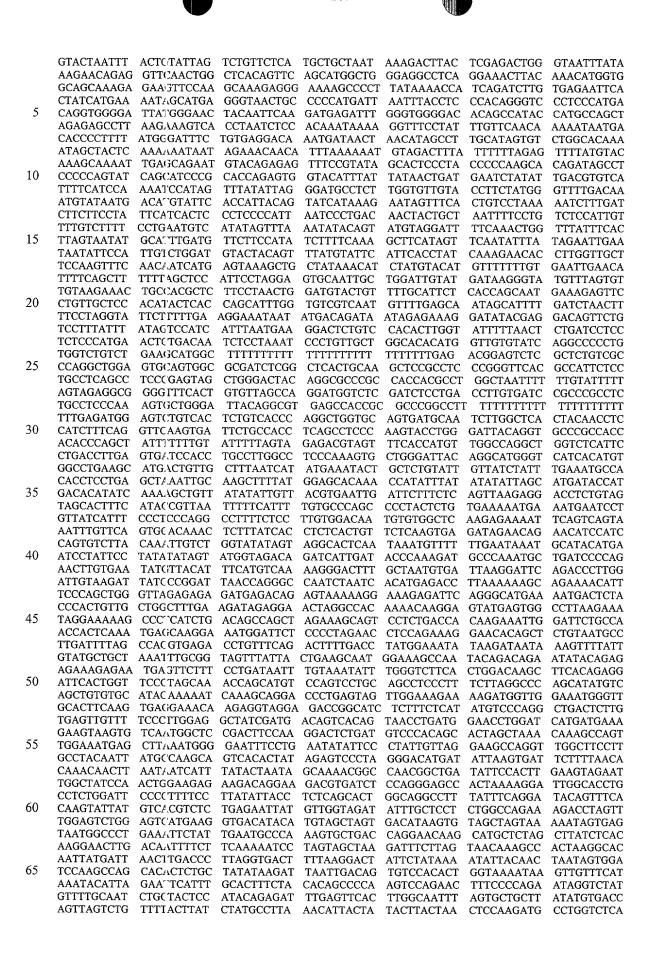


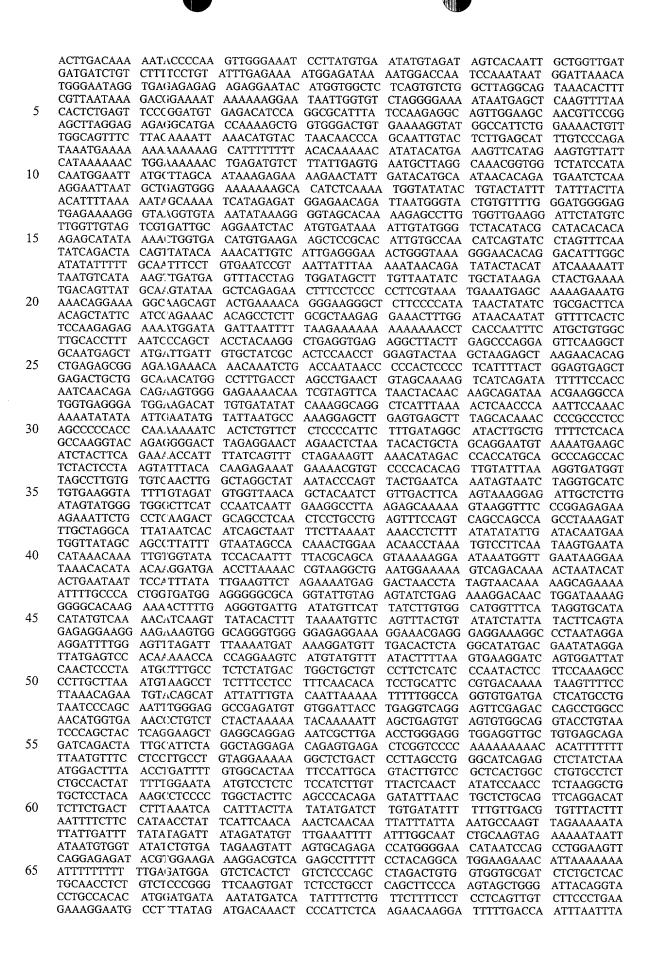


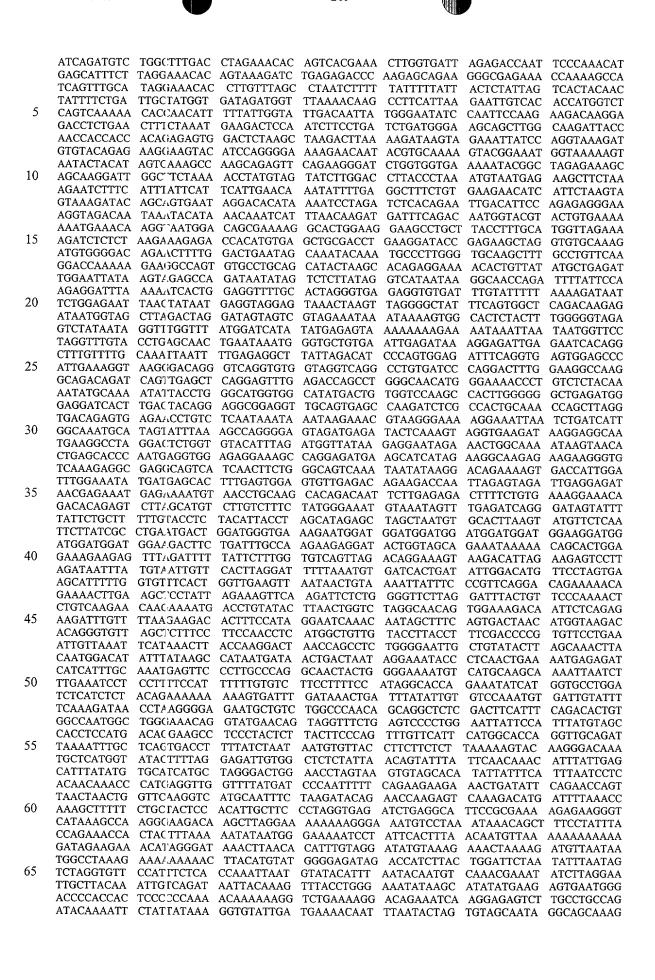


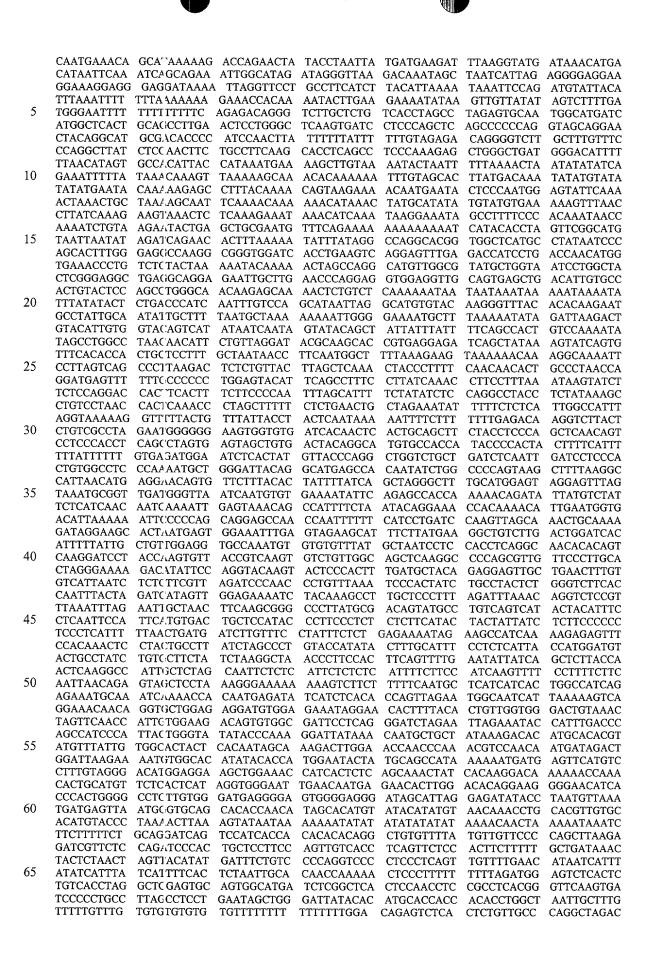


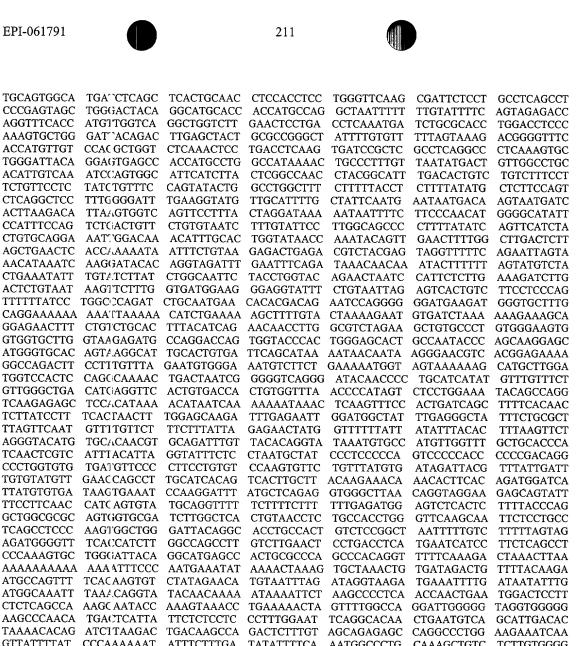




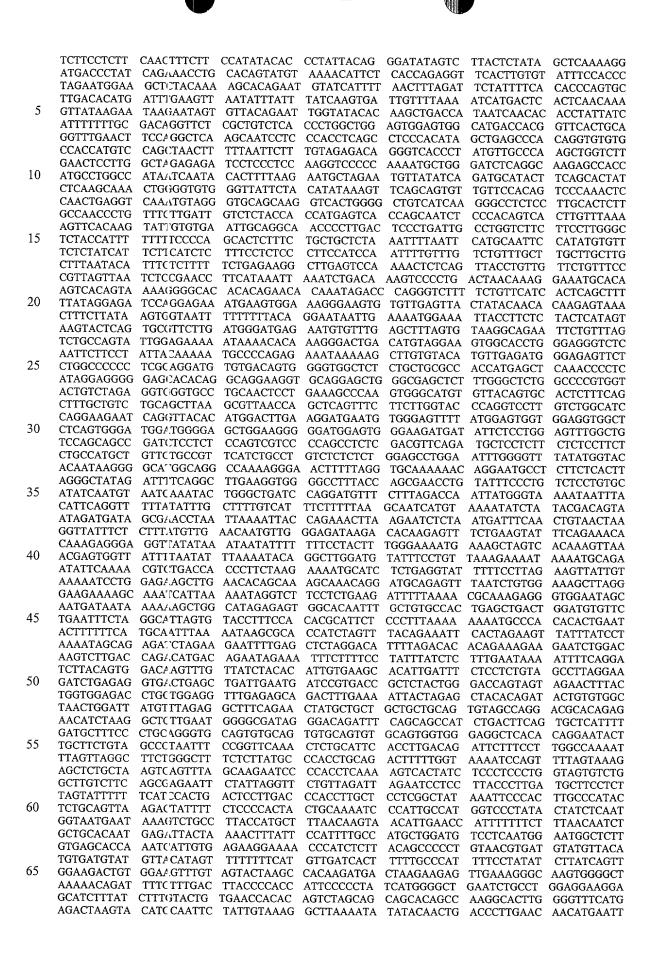


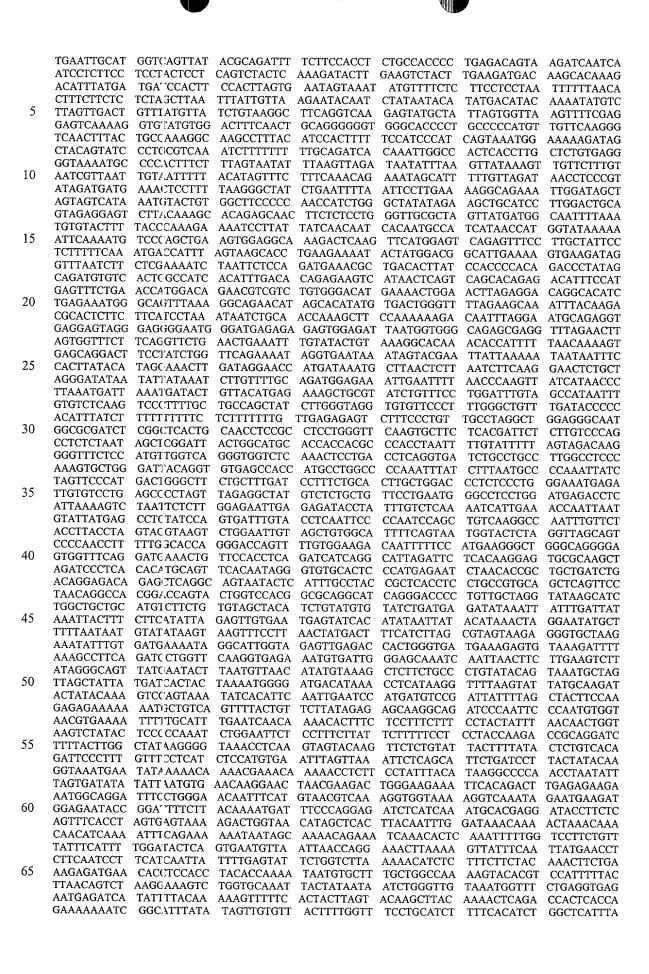


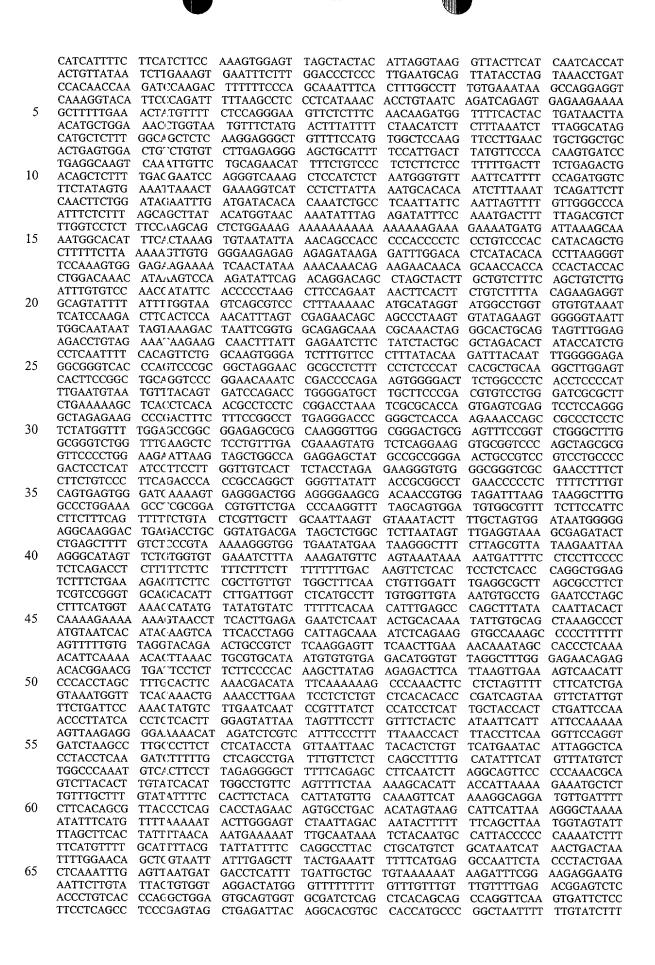


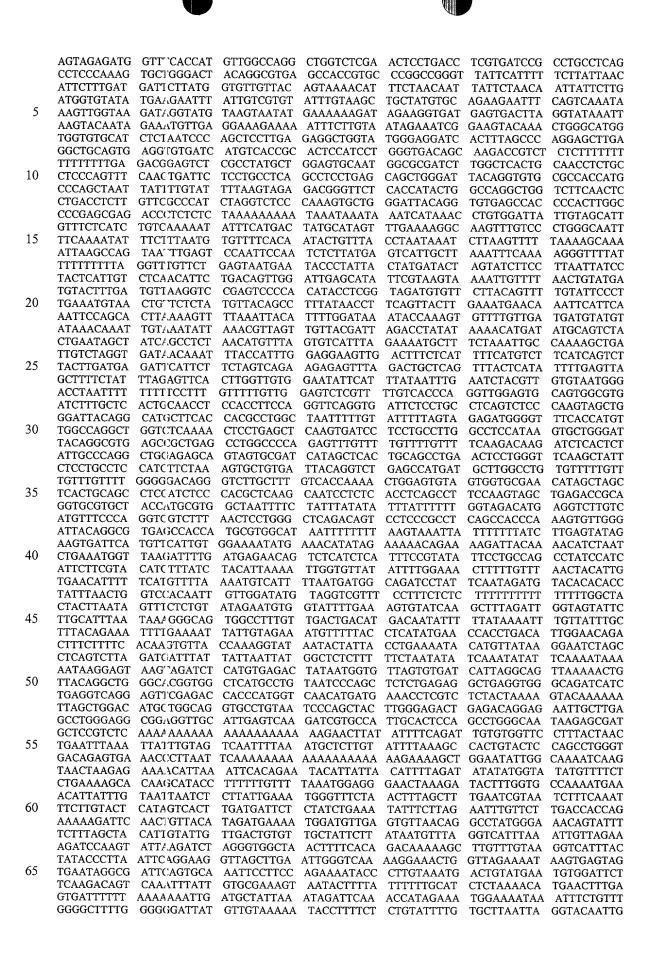


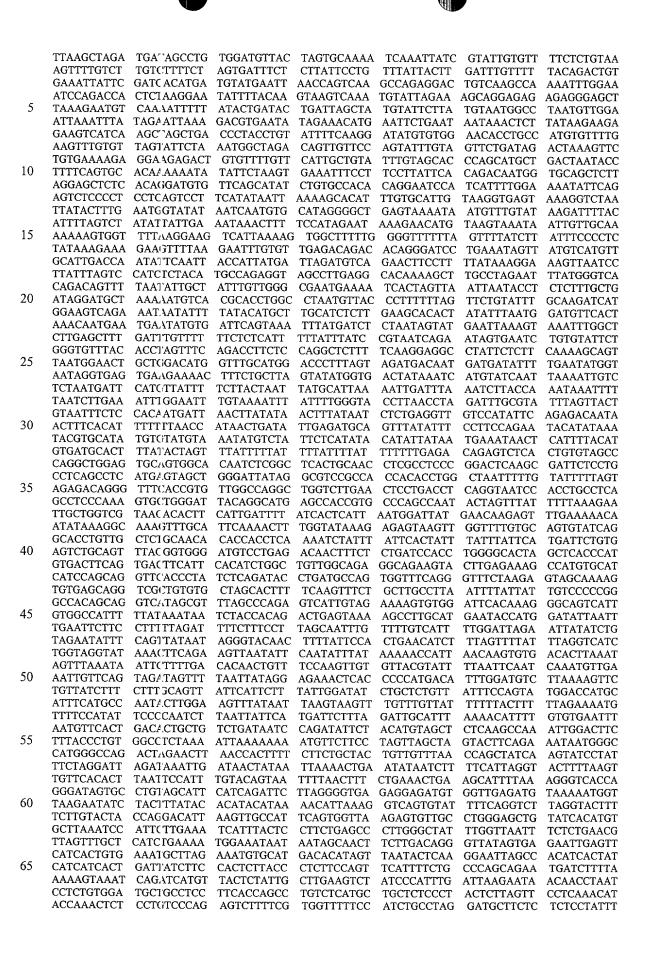
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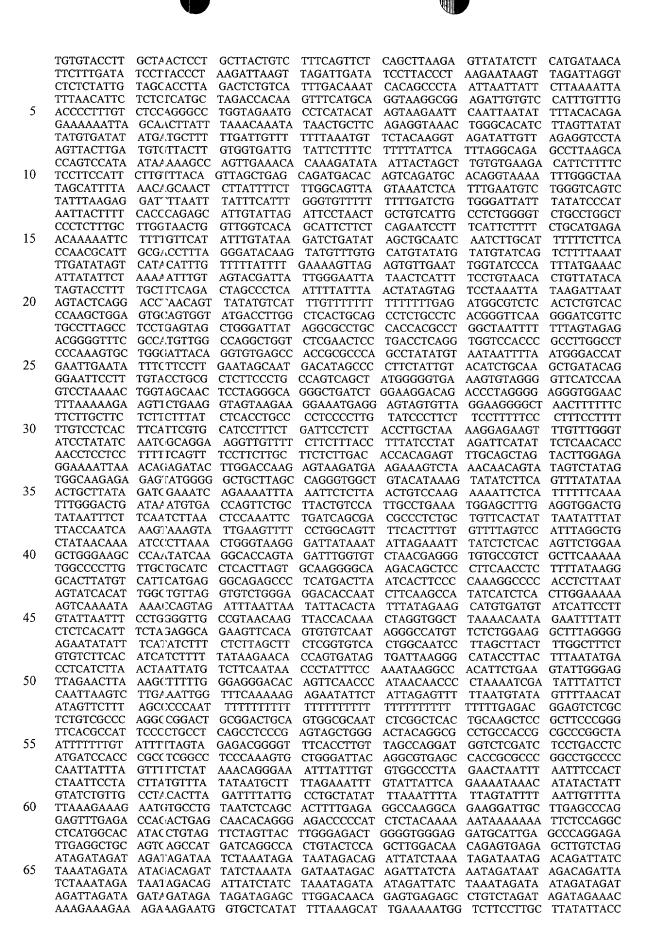


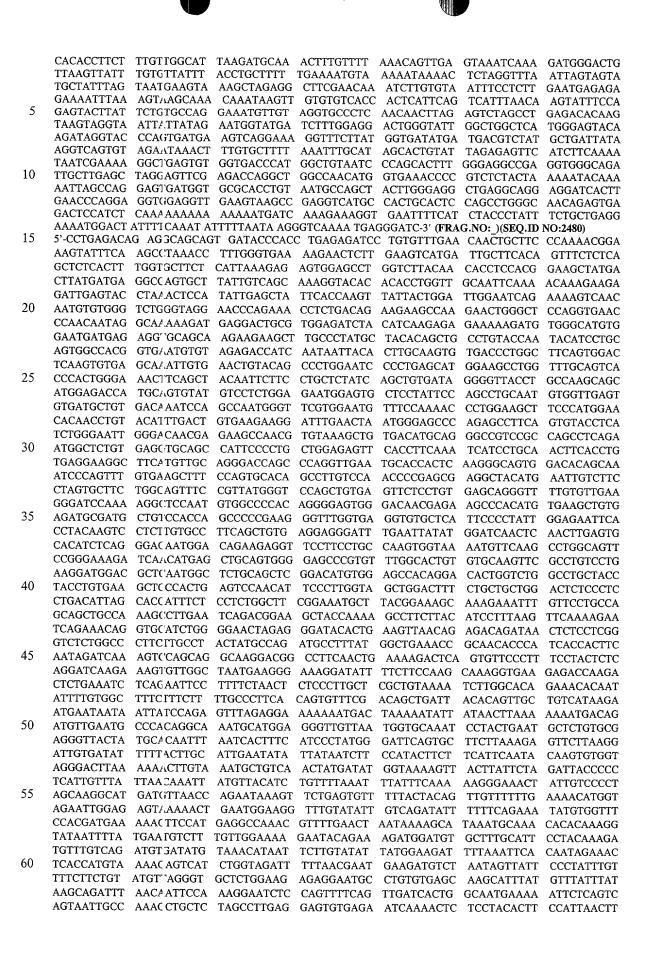














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TCAGACCTAT TTGACATAAC ACTATAAAGG TTGACAATAA ATGTGCTTAT GTTT-3'(FRAG.NO: )(SEQ.ID NO:2479)

5'-CCT TGC CTG CTG G-3' (FRAG. NO: 1739) (SEQ. ID NO: 1752)

5'-GTT GTC CC-3' (FRAG. NO: 1740) (SEQ. ID NO:1753)

5'-GTT CTT GGC TTC "TC TGT C-3' (FRAG. NO:1080) (SEQ. ID NO:1088)

5'-GGC TGG TGG-3' (F RAG. NO:1083) (SEQ. ID NO:1092)

5'-CGT TGG CTT CTC (FTT GTC CC-3' (FRAG. NO:1081) (SEQ. ID NO:1089)

5'-TGT GGG CTT CTC '3TT GTC CC-3' (FRAG. NO:1082) (SEQ. ID NO:1090)

5'-CCC TTC GGG GGC TGG TGG-3' (FRAG. NO:1083) (SEQ. ID NO:1091)

5'-GGC CGT CCT TGC CTG CTG G-3' (FRAG. NO:1084) (SEQ. ID NO:1093)

#### **Human P Selectin Fragments**

TTT CTT TTC-3' (FRAG. NO: 1741) (SEQ. ID NO: 1754)

5'-TCC TTT CTT TTC-3' (FRAG. NO: 1742) (SEQ. ID NO: 1755)]

5'-CTC CTT TT-3' (FRAG. NO:1743) (SEQ. ID NO:1756)

5'-TTT TCT CTT TCG (TT TCT TTT CGT CTC CTG TTC CTC CTT TT-3'(FRAG.NO:1085)(SEQ. ID NO:1094) 5'-TTG CTG TTT TTT (TC CTT CTT CTC TCT TTT CTT TTC-3' (FRAG. NO:1086) (SEQ. ID NO:1095)

# **Human Endothelial Monocyte Activating Factor**

## Nucleic Acid & Antisense Oligonucleotide Fragments

TTT CTT TTC-3' (FRAG. NO: 1744) (SEQ. ID NO: 1757)

5' -CC TTT CTT TTC (I'RAG. NO: 1745) (SEQ. ID NO: 1758)

5'-CTG TTC CTC CTT "T-3' (FRAG. NO:1746) (SEQ. ID NO:1759)

5'-TTT TCT CTT TCG ('TT TCT TTT CGT CTC CTG TTC CTC CTT TT-3'(FRAG.NO:1087)(SEQ. ID NO:1096)

5'-TTG CTG TTT TTT ('TC CTT CTT CTC TCC TTT CTT TTC-3' (FRAG. NO:1088) (SEQ. ID NO:1097)

## Human IL3\* Nucle c Acid and Antisense Oligonucleotide Fragments

GGB GTT GGB GCB GGB GGB GGB GGC GGC TCB TGT TTG GBT CGG CBG GBG GCB CTC (FRAG. NO: 1747) (SEQ. ID NO: 1750)]

5'-G GBG GCB CTC-3' (FRAG. NO: 1748) (SEQ. ID NO: 1761)

5'-GT GGG GCT CTG-3 (FRAG. NO:1749) (SEQ. ID NO:1762)

HUMIL3AAS1: 5'-CTC "GT CTT GTT CTG GTC CTT CGT GGG GCT CTG-3' (FRAG.NO:1089)(SEQ.ID NO:1098) HUMIL3AAS2: 5'-TGT (CGC GTG G GTG CGG CCG TGG CC-3' (FRAG. NO:1090) (SEQ. ID NO:1099)

GGC GGB CCB GGB GT T GGB GCB GGB GGB GGB GGG GGC GGC TCB TGT TTG GBT CGG CBG GBG GCB CTC (FRAG. NO:1091) (SEQ. ID NO:1100)

#### Human IL3 Recept or Nucleic Acid and Antisense Oligonucleotide Fragments

5'-TCT GGG GTG TCC TGG CCT TCG TGG TTC CTC TTC CTT CGT TTG CCG TCC GCG GGG GCC CCC GGG CCT TC CTC CTG GTC GC3 CTT GTC GTT TTG GGG CCG GCT TTG CCC GCC TCC CGG CGC CTG GCC CGG CC TTC CTG GGC TGC GTG CFC GTT CTG TTC TTC CTG GCT CTG GGG TGT CCT GGC CTT CGT GGT TCC TCT TCC

- TTC GTT TGC CGT CCG CGG GGG CCC CCG GGC CT GGC TGC GCT CCT GCC CCG CCT CTT TCC CGG GCT CTT GGA GAC AGG GCA CGG CGA TCA GGA GCA GCG TGA GCC AAA GGA GGA CCA TCG GGA ACG CAG CTC CGG AAC GCA GGA CAG AGG TGC C GC BGG BGB CBG GGC BGG GCG BTC BGG BGC BGC GTG BGC CBB BGG BGG
- BCC BTC GGG BBC GCB GCT CCG GBB CGC BGG BCB GBG GTG CC-3' (FRAG. NO: 1750) (SEQ. ID NO: 1763)

GBG GTG CC-3' (FRAG. NO: 1751) (SEO. ID NO: 1764)

- 5'- GCC CCG C-3' (FRAG. NO:1752) (SEQ. ID NO:1765)
- 5'-TCTGGGGTGTCCTG (FRAG. NO:1092) (SEQ. ID NO:1101)
- 5'-GCCTTCGTGGTTCC (FRAG. NO:1093) (SEQ. ID NO:1102)
- 55 5'-TCTTCCTTCGTTTGC (FRAG. NO:1094) (SEQ. ID NO:1103)
  - 5'-CGTCCGCGGGGCCCCCGGGCCT (FRAG. NO:1095) (SEQ. ID NO:1105)
  - 5'-GGC TGC GCT CCT GCC CCG C (FRAG. NO:1096) (SEQ. ID NO:1104)



- 5'-CTCTTTCCCGGGCTCTT (FRAG. NO:1097) (SEO. ID NO:1106)
- 5'-GCGCTGGGGGGTGCTCC (FRAG. NO:1098) (SEO. ID NO:1107)
- 5'-CGTGTGTTTTGCGCC'CTCCTCCTGGTCGC (FRAG. NO:1099) (SEQ. ID NO:1108)
- 5'-GCTTGTCGTTTTGC (FRAG. NO:1100) (SEQ. ID NO:1109)
- 5 5'-GGCCGGCTTTGCCCGCCTCCC (FRAG. NO:1101) (SEQ. ID NO:1110)
  - 5'-GGCGCCTGGCCCGGCC (FRAG. NO:1102) (SEQ. ID NO:1111)
  - 5'-TTCCTGGGCTGCGT'GCGC (FRAG. NO:1103) (SEQ. ID NO:1112)
  - 5'-GTTCTGTTCTTCTTCCTGGC (FRAG. NO:1104) (SEQ. ID NO:1113)
  - 5'-GCB GGB GBC BGG GCB GGG CGB TCB GGB GCB GCG TGB GCC BBB GGB GGB CCB TCG GGB BCG CBG CTC
- 10 CGG BBC GCB GGB 5' CBG BGG TGC C (FRAG. NO:1105) (SEQ. ID NO:1114)

# Human IL-4 Nucleic Acid and Antisense Oligonucleotide Fragments

5'-CTC TGG TTG GCT TCC TTC GCC GGC BCB TGC TBG CBG GBB GBB CBG BGG GGG BBG CBG TTG GGB GGT GBG BCC CBT TBB TBG GTG TCG B-3' (FRAG. NO: 1753) (SEQ. ID NO: 1766)

5'-GCC GGC BCB-3' FRAG. NO: 1754) (SEQ. ID NO: 1767)

15 5'-T TCC TTC-3' (FRAG. NO:1755) (SEQ. ID NO:1768)

5'-CTC TGG TTG GCT TCC TTC-3' (FRAG. NO:1106) (SEQ. ID NO:1115)

5'-GCCGGCBCBTGCTEGCBGGBBGBBCBGBGGGGBBGCBGTTGGGBGGTGBGBCCCBTTBBTBGGTGTCGB-3' (FRAG. NO:1107) (SEQ. ID NO:1116)

#### Human IL4 Receptor Nucleic Acid and Antisense Oligonucleotide Fragment

- GTC GGC TGG CTG CTG CTT CGG GCC GCC TGG GCT TCC CTG TGC CCC TTT CCT CTG GGT CCC CCT CCC GTT CCA AGC TGC ACC GCA CAG ACC GGC GCT ACA GGA CAG AGC CAG GCA AGC ACC CAT GGG GAT CCA GGC CCA GCT GTT CCB BGC TGC BCC GCB CBG BCC GGC GCT BCB GGB CBG BGC CBG GCB BGC BCC CBT GGG GBT CCB GGC CCB GCT G -3'(FRAG. NO: 1756)(SEQ ID NO:1769)
  - 5'-TCTGCGC-3' (FRA G. NO: 1757) (SEQ ID NO: 1770)
- 30 5'-CCT GCT CCT GGG G (FRAG. NO:1758) (SEQ. ID NO:1771)
  - 5'-TCTGCGCGCCCCTC CTCC (FRAG. NO:1108) (SEQ. ID NO:1117)
  - 5'-CGCCCGGCTTCTCI (FRAG. NO:1109) (SEQ. ID NO:1118)
  - 5'-CGTGTGGGCTTCG(; (FRAG. NO:1110) (SEQ. ID NO:1119)
  - 5'-CCCCGCGCCTCCGTTGTTCTC (FRAG. NO:1111) (SEQ. ID NO:1120)
- 5'-TGCTCGCTGGGCTTG (FRAG. NO:1112) (SEQ. ID NO:1121)
  - 5'-GGTTTCCTGGGGCC'CTGGGTTTC (FRAG. NO:1113) (SEQ. ID NO:1122)
  - 5'-TCTGCCGGGTCGTTTTC (FRAG. NO:1114) (SEQ. ID NO:1123)
  - 5'-GGGTGCTGCCG (FRAG. NO:1115) (SEO. ID NO:1124)
  - 5'-CTTGGTGCTGGGGCTCC (FRAG. NO:1116) (SEQ. ID NO:1125)
- 40 5'-GGCGGCTGCGGGCTGGGTTGGG (FRAG. NO:1117) (SEQ. ID NO:1126)
  - 5'-CTTGGCTGGTTCCTGGCCTCGGG (FRAG. NO:1118) (SEQ. ID NO:1127)
  - 5'-CCTCCTCCTCCTCCTCGCTCCCTTTTTCTTCCTCT (FRAG, NO:1119) (SEQ. ID NO:1128)
  - 5'-TCCCTGCTGCTCTC (FRAG. NO:1120) (SEQ. ID NO:1129)
- 5'-TGCCCTCCCTCCCTCGG (FRAG. NO:1121) (SEQ. ID NO:1130)
- 45 5'-GGTGCCTCCTTGGCCCCTGC (FRAG. NO:1122) (SEQ. ID NO:1131)
  - 5'-GGCTGCTCCTTGCCCC (FRAG. NO:1123) (SEQ. ID NO:1132)
  - 5'-CTCTGGGTCGGGCTGGC (FRAG. NO:1124) (SEQ. ID NO:1133)
  - 5'-GGGGCGTCTCTGTC'C (FRAG. NO:1125) (SEQ. ID NO:1134)
  - 5'-CTGGCCTGGGTGCC (FRAG. NO:1126) (SEQ. ID NO:1135)
- 50 5'-GCCTCTCCTGGGGCGGTGGCTCCCTGTCC (FRAG. NO:1127) (SEQ. ID NO:1136)
  - 5'-CCTTTTCCCCCGGCTCC (FRAG. NO:1128) (SEQ. ID NO:1137)
  - 5'-GTGGGGGCTTTGGC (FRAG. NO:1129) (SEQ. ID NO:1138)
  - 5'-GGG GGT CTG TGG CCT GCT CCT GGG G (FRAG. NO:1130) (SEQ. ID NO:1139)
  - 5'-AGGGGTCTGGGGCCCTC (FRAG. NO:1131) (SEO. ID NO:1140)
- 55 5'-TTTTGGGGGTCTGC CTTG (FRAG. NO:1132) (SEQ. ID NO:1141)
  - 5'-GCCTGGCTGCCTTCC (FRAG. NO:1133) (SEQ. ID NO:1142)
  - 5'-GGGGCCTGCCGTGGGGC (FRAG. NO:1134) (SEQ. ID NO:1143)
  - 5'-TGTCCTCTGTTGCTCCCCTT (FRAG. NO:1135) (SEQ. ID NO:1144)
  - 5'-TGCCTGCTGTCTGG (FRAG. NO:1136) (SEQ. ID NO:1145)
- 60 5'-GGTTCCCGCCTTCCCT (FRAG. NO:1137) (SEQ. ID NO:1146)



5'-GTT CCC AGA GCT TGC CAC CTG CAG CAG GAC CAG GCA GCT CAC AGG GAA CAG GAG CCC AGA GCA AAG CCA CCC CAT TGG GAG ATG CCA AGG CAC CAG GCT G (FRAG. NO:1138) (SEQ. ID NO:1147)
5'-GTT CCC BGB GCT TGC CBC CTG CBG CBG GBC CBG GCB GCT CBC BGG GBB CBG GBG CCC BGB GCB BBG CCB CCC CBT TGG GEG BTG CCB BGG CBC CBG GCT G-3' (FRAG. NO:1139) (SEQ. ID NO:1148)

#### 5 Human IL5\* Nucleic Acid and Antisense Oligonucleotide Fragments

5'-TCCCTGTTTC CCCCCTTTCG TTCTGCGTTT GCCTTTGGCG TTTTTTGTTT GTTTCTCT TCCGTCTTTC TTCTCCCCT GTGGGB3TTT CTGTGGGGBT GGCBTBCBCG TBGGCBGCTC CBBGBGCTBG CBBBCTCBBB TGCBGBBGCB TCCTCBTGGC TCTGBBBCGG TGGGAATTTC TGTGGGGBTG GCATACACGT AGGCAGCTCC AAGAGCTAGC AAAC `CAAAT GCAGAAGCATC CTCATGGCTC TGAAACG-3' (FRAG. NO: 1759) (SEQ. ID NO:

10 1772)

5'-GCC CCG GG-3' (FRAG. NO: 1760) (SEQ. ID NO: 1773) 5'-G GGT TTC T-3' (FRAG. NO: 1761) (SEQ. ID NO: 1774) 5'-GTG GGG BTG GC-3' (FRAG. NO: 1762) (SEQ. ID NO: 1775) 5'-CCB BGB GCT BGC-3' (FRAG. NO: 1763) (SEQ. ID NO: 1776)

- 5'-TCC CTG TTT CCC CCC TTT-3' (FRAG. NO:1140) (SEQ. ID NO:1149)
   5'-CGT TCT GCG TTT GCC TTT GGC-3' (FRAG. NO:1141)(SEQ. ID NO:1150)
   5'-GTT TTT TGT TTG T'TT TCT-3' (FRAG. NO:1142)(SEQ. ID NO:1151)
   5'-CTC TCC GTC TTT CTT CTC C-3' (FRAG. NO:1143) (SEQ. ID NO:1152)
   5'-CCT CCT GCC TGT GTC CCT GCT CCC C-3' (FRAG. NO:1144) (SEQ. ID NO:1153)
- 5'-GAG GGT TTC TGG CTT CCT CTC T-3' (FRAG. NO:1145) (SEQ. ID NO:1154)
   5'-TGT CTC TCT GTC (CTT TTG TT-3' (FRAG. NO:1146) (SEQ. ID NO:1155)
   5'-TGT TGT GCG GCC TGG TGC CCT GCC CCG GG-3' (FRAG. NO:1147) (SEQ. ID NO:1156)
   5'-GTG GGA ATT TCT GTG GGG BTG GCA TAC ACG TAG GCA GCT CCA AGA GCT AGC AAA CTC AAA TGC AGA AGC ATC CTC ATG GCT CTG AAA CG-3' (FRAG. NO: 1764) (SEQ. ID NO: 1777)
- 25 5'-GTG GGB BTT TCT 5TG GGG BTG GCB TBC BCG TBG GCB GCT CCB BGB GCT BGC BBB CTC BBB TGC BGB BGC BTC CTC BTG GCT CTG BBB CG-3' (FRAG. NO:1148) (SEQ. ID NO:1157)

## Human IL-5 Receptor Nucleic Acid and Antisense Oligonucleotide Fragments

5 5'-TTCCTTTGCTCTTG-3' (FRAG. NO:1150) (SEQ. ID NO:1159)
5'-GTGTGTCTTTGCTCT-3' (FRAG. NO:1151) (SEQ. ID NO:1160)
5'-GCCCTGCCTCTCTC C-3' (FRAG. NO:1152) (SEQ. ID NO:1161)
5'-CT CBGTGGCCCC (BBBBGGBTG BGTBBTBCBT GCGCCBCGBT GBTCBTBTCC TTTTTBCTBT GBGG (FRAG. NO: 1768) (SEQ. ID NO: 1781)

#### 40 Human IL-6 Receptor Fragments

- 55 5'-GGCCBGCBGG-3' (FRAG. NO:1186) (SEQ. ID NO:1195)
  - 5'-GCBGCCBGCBGCG-3' (FRAG. NO: 1770) (SEQ. ID NO: 1783)
  - 5'-C GCBGCCGBCGGCC -3' (FRAG. NO: 1771) (SEQ. ID NO: 1784)
  - 5'-GGGGGTGGCTTCC'IGCC3'- (FRAG. NO:1153) (SEQ. ID NO:1162)
  - 5'-GCGTCTCTGGGCCGTCCC-3' (FRAG. NO:1154) (SEQ. ID NO:1163)



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5'-GTCCCTCGGCCCCCCCGCGCTCGGCTCCTCTCCC-3' (FRAG. NO:1155) (SEQ. ID NO:1164)
     5'-TCTGGCCCGGCTC-3' (FRAG. NO:1156) (SEQ. ID NO:1165)
     5'-GGGGCGGGGGGGGGGGGGGGC-3' (FRAG. NO:1157) (SEQ. ID NO:1166)
     5'-GGCGCTGCCCTGCGC-3' (FRAG. NO:1158) (SEQ. ID NO:1167)
    5'-GCGGCGCTGGCCCC'-3' (FRAG. NO:1159) (SEQ. ID NO:1168)
     5'-TGCTGGCCGTCGGCTGCGCTGCTGCCCT-3' (FRAG. NO:1160) (SEQ. ID NO:1169)
     5'-GCTGGCCGCGCGGG-3' (FRAG. NO:1161) (SEQ. ID NO:1170)
    5'-GCCTGTCCGCCTCTGCGGG-3' (FRAG. NO:1162) (SEQ. ID NO:1171)
5'-CGCTGTCTCCTGGC-3' (FRAG. NO:1163) (SEQ. ID NO:1172)
5'-TTGTCTTCCGGCTCT-3' (FRAG. NO:1164) (SEQ. ID NO:1173)
5'-TCTGCTGGGGGTGGG-3' (FRAG. NO:1165) (SEQ. ID NO:1174)
     5'-GCTGGGCGGCCGGCCCGGT-3' (FRAG. NO:1166) (SEQ. ID NO:1175)
     5'-GCTGGGGCTCCTCGGGGGG-3' (FRAG. NO:1167) (SEO. ID NO:1176)
     5'-GGGGGCTCTTCCG(i-3' (FRAG. NO:1168) (SEQ. ID NO:1177)
    5'-GCTGTCTCCCTCCGGG-3' (FRAG. NO:1169) (SEQ. ID NO:1178)
     5'-GCGGGGGTTTCTGGCC-3' (FRAG. NO:1170) (SEQ. ID NO:1179)
     5'-GTGGGGGTCTTGCC-3' (FRAG. NO:1171) (SEQ. ID NO:1180)
     5'-TGGCCTCCGGGCTC'C-3' (FRAG. NO:1172) (SEQ. ID NO:1181)
     5'-TGCTTGTCTTGCCTTCCTTC-3' (FRAG. NO:1173) (SEQ. ID NO:1182)
    5'-TCTGGTCGGTTGTCGCTCG-3' (FRAG. NO:1174) (SEQ. ID NO:1183)
    5'-GGGCTCCGTGGGTCCCTGGC-3' (FRAG. NO:1175) (SEQ. ID NO:1184)
     5'-GCCCGTTTGTGTTTTGTC-3' (FRAG. NO:1176) (SEQ. ID NO:1185)
     5'-TTTTCCCCTGGCGT-3' (FRAG. NO:1177) (SEQ. ID NO:1186)
    5'-CCCTGTGCCCCTCTCCTCCTCCTCTCTCTCTC-3' (FRAG. NO:1178) (SEQ. ID NO:1187)
    5'-GCTCTCCTTTGTGGG-3' (FRAG. NO:1179) (SEQ. ID NO:1188)
    5'-GCCCTCCCTGCTGCT-3' (FRAG. NO:1180) (SEQ. ID NO:1189)
    5'-CTTGGTTTTGGGCT-3' (FRAG. NO:1181) (SEQ. ID NO:1190)
    5'-TTTTTTCTCTCCTCCTTTTTC-3' (FRAG. NO:1182) (SEQ. ID NO:1191)
    5'-GTGCGTGGGCCTCC'-3' (FRAG. NO:1183) (SEQ. ID NO:1192)
    5'-GCACGCCTCT TGCCACCTCC TGCGCAGGGC AGCGCCTTGG GGCCAGCGCC GCTCCCGGCG CGGCCAGCAG
     GGCAGCCAGC AGCGCGCAGC CGACGGCCAG CATGCTTCCT CCTCGGCTAC CACTCCATGG TCCCGCAGAG
     GCGGACAGGC-3' (FRAG. NO:1185) (SEO. ID NO:1194)
     5'-GCBCGCCTCT TGCCBCCTCC TGCGCBGGGC BGCGCCTTGG GGCCBGCGCC GCTCCCGGCG CGGCCBGCBG
     GGCBGCCBG CBGCGCGBG CCGBCGGCCB GCBTGCTTCC TCCTCGGCTB CCBCTCCBTG GTCCCGCBGB
35
     GGCGGBCBGG C-3' (FRAG. NO:1187) (SEQ. ID NO:1196)
     Human IL-6 Nucleic Acid and Antisense Oligonucleotide Fragments
     5'-GGGGGTGGCT TCCTGCCGCG TCTCTGGGCC GTCCCGTCCC TCGGCCCCGC GCCGCGCTCG GCTCCTCTCC
     GCTGGCCGTC GGCTGCGCGC TGCTGGCTGC CCTGCTGGCC GCGCCGGGGC CTGTCCGCCT CTGCGGGCGC
     40
     GCCTCCGGGC TCCTGCTTGT CTTGCCTTCC TTCTCTGGTC GGTTGTGGCT CGGGGCTCCG TGGGTCCCTG
    45
     CGGCCAGCAG GGCAGCCAGC AGCGCGCAGC CGACGGCCAG CATGCTTCCT CCTCGGCTAC CACTCCATGG
     TCCCGCAGAG GCGGACAGGC GCBCGCCTC TTGCCBCCTC CTGCGCBGGG CBGCGCCTTG GGGCCBGCGC CGCTCCCGGC GCGGCCBGCB GGGCBGCCBG CCBCGCCCB GCBTGCTTCC TCCTCGGCTB
     CCBCTCCBTG GTCCCGCBGB GGCGGBCBGG C-3' (FRAG. NO:1772) (SEQ. ID NO:1785)
     5'-GGGGCBGG-3' (FRAG. NO:1773) (SEQ. ID NO:1786)
     5'-GBBGGCBG CBGGC 3' (FRAG. NO:1774) (SEQ. ID NO:1787)
     5'-CCBGGBGCBG CCCC-3' (FRAG. NO:1775) (SEQ. ID NO:1788)
     5'-BGGG BGBBGGCBBC-3' (FRAG. NO:1776) (SEQ. ID NO:1789)
     5'-GCT TCT CTT TCG 'TC CCG GTG GGC TCG-3' (FRAG. NO:1188) (SEQ. ID NO:1197)
    5'-GTG GCT GTC TGT GTG GGG CGG CT-3' (FRAG. NO:1189) (SEQ. ID NO:1198)
     5'-GTG CCT CTT TGC 'TGC TTT C-3' (FRAG. NO:1190) (SEQ. ID NO:1199)
     5'-GAT TCT TTG CCT 'TTT TCT GC-3' (FRAG. NO:1191) (SEQ. ID NO:1200)
     5'-CTCCTGGGGG TBCTGGGGCB GGGBBGGCBG CBGGCBBCBC CBGGBGGCBC CCCBGGGBGB BGGCBBCTGG BCCGBBGGCG
     CTTGTGGBGB BGGBGTT: DBT BGCTGGGCTC CTGGBGGGGB GBTBGBGC-3' (FRAG., NO:1777) (SEO.ID NO:1790)
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60 Human Monocyte-derived Neutrophil Chemotactic Factor



## Nucleic Acid and Antisense Oligonucleotide Fragments

5'-GGGGTGGBBB GGTTTGGBGT BTGTCTTTBT GCBCTGBCBT CTBBGTTCTT TBGCBCTCCT TGGCBBBBCT GCBCCTTCBC BCBGBGCTGC BGBBBTCBGG BBGGCTGCCB BGBGBGCCBC GGCCBGCTTG GBBGTCBTGT TTBCBCBCBG TGBGBTGGTT CCTTCCGGGC TTGTGTGCTC TGCTGTCTCT TGGTTCCTTC CGGTGGTTTC

- TTCCTGGCTC TTGTCCTTTC TCTTGG CCCT TGGC-3' (FRAG. NO:1778) (SEQ. ID NO: 1791)
  - 5'-GGBGT BTG-3' (FRAG. NO:1779) (SEQ. ID NO: 1792)
  - 5'-GCBCTGBCBT CT-3' (FRAG. NO:1780) (SEQ. ID NO:1793)
  - 5'-CCG GTG G-3' (FRAG. NO:1781) (SEQ. ID NO: 1794)
  - 5'-GG CCC TTG GC-3' (FRAG. NO:1782) (SEQ. ID NO: 1795)
- 5'-GCT TGT GTG CTC 'IGC TGT CTC T-3' (FRAG. NO:1192) (SEQ. ID NO:1201)
  - 5'-TGG TTC CTT CCG GTG GTT TCT TCC TGG CTC TTG TCC T-3' (FRAG. NO:1193) (SEQ. ID NO:1202)
  - 5'-TTC TCT TGG CCC TG GC-3' (FRAG. NO:1194) (SEQ. ID NO:1203)
  - 5'-GGGGTGGBBB GGTTTGGBGT BTGTCTTTBT GCBCTGBCBT CTBBGTTCTT TBGCBCTCCT TGGCBBBBCT GCBCCTTCBC BCBGBGC-3' (FRAG. NO:1783) (SEO. ID NO: 1796)
- 15 Human Neutrophil Elastase (Medullasin) Nucleic Acid and Antisense Oligonucleotide Fragments
  - 5'-GGGCTCCCGC CG:JGBGBGGT TBTGGGCTCC CBGGBCCBCC CGCBCCGCGC GGBCGTTTBC BTTCGCCBCG CBGTGCGCGG CCGI-CBTGBC GBBGTTGGGC GCBBTCBGGG TGGCGCCGCB GBBGTGGCCT CCGCGCBGCT GCBGGGBCBC CBTGBBGGGC CBCGCGTGGG GCCGCGCTCG CCGGCCCCCC BCBBTCTCCG BGGCCBGCGC GGTGCCCCC BGCBGCBGG CCGGCBGGBC BCBGGCGBGG BGBCBCGCGB GTCGGCGGCC GBGGGTCBTG
- 20 GTGGGGCTGG GGC CCGGGG TCTCTGCCCC TCCGTGCTGG TGGGGCTGGG GCTCCGGGG TCTCTGCCCC TCCGTGCCGC GTGGGGCCGC GCTCGCCGGC CCCCCCTGC CGGGTGGGCT CCCGCCGCGC GCCGGCCTGC CGGCCCCTCG TGGGTCCTGC TGGCCGGGTC CGGGTCCCGG GGGTGGGGCG CGBGTCGGCG GCCGBGGGTC-3' (FRAG. NO:1784) (SE(). ID NO: 1797)
  - 5'-GG TGG GGC-3' (I'RAG. NO:1785) (SEQ. ID NO: 1798)
- 5'-G GGG CCG -3' (F RAG. NO:1786) (SEQ. ID NO:1799)
  - 5'- GGC CGG GTC CGC G-3' (FRAG. NO:1787) (SEQ. ID NO: 1800)
  - 5'-TGG TGG GGC TGG GGC TCC GGG GTC TCT GCC CCT CCG TGC-3' (FRAG.NO:1195)(SEQ.ID NO:1204)
  - 5'-CGC GTG GGG CCG CGC TCG CCG GCC CCC C-3' (FRAG. NO:1196) (SEQ. ID NO:1205)
  - 5'-CCT GCC GGG TGG GCT CCC GCC GCG-3' (FRAG. NO:1197) (SEQ. ID NO:1206)
- 5'-CGC CGG CCT GCC GGC CCC TC-3' (FRAG. NO:1198) (SEQ. ID NO:1207)
  - 5'-GTG GGT CCT GCT 3GC CGG GTC CGG GTC CCG GGG GTG GGG-3'(FRAG.NO:1199)(SEQ.ID NO:1208)
  - 5'-CGC GBG TCG GCG GCC GBG GGT C-3' (FRAG. NO:1200) (SEQ. ID NO:1209)
  - 5'-GGGCTCCCGC CGCGBGBGGT TBTGGGCTCC CBGGBCCBCC CGCBCCGCGC GGBCGTTTBC BTTCGCCBCG CBGTGCGCGG CCGECBTGBC GBBGTTGGGC GCBBTCBGGG TGGCGCCGCB GBBGTGGCCT CCGCGCBGCT GCBGGGBCBC CBTGBBGGGC CBCGCGTGGG GCCGCGCTCG CCGGCCCCCC BCBBTCTCCG BGGCCBGCGC GGTGCCCCCC BGCBGCBBGG CCGGCBGGBC BCBGGCGBGG BGBCBCGCGB GTCGGCGGCC GBGGGTCBTG GTGGGGCTGG GGCT('CGGGG TCTCTGCCCC TCCGTGC-3' (FRAG. NO:1788) (SEO. ID NO: 1801)

## Human Neutrophil Oxidase Factor Nucleic Acid and Antisense Oligonucleotide Fragments

- 5'-CGGGBGTGGG GGTCCTGGBC GGCBCTGBBG GCBTCCBGGG CTCCCTTCCB GTCCTTCTTG TCCGCTGCCB GCBCCCCTTC BTTCCBGBGG CTGBTGGCCT CCBCCBGGGB CBTGBTTBGG TBGBBBCTBG GBGGCCGGCC GGGGCTGCTG CTGGGCTCTT CTTTTTGTTT CTGGCCTGGT GCTCTCTCGT GCCCTTTCCC TTGGGTGTCT TGTTTTTGTG GCCTCCBCCB GGGBCBTG-3' (FRAG. NO:1789) (SEO. ID NO: 1802) 5'-CGGGBGTGGG GG-3' (FRAG.NO:1790) (SEQ. ID NO: 1803)
- 5'-GCCBGCBCCCC-3' (FRAG.NO:1791) (SEQ. ID NO: 1804)
- - 5'-C CBC CBG-3' (FRAG.NO:1792) (SEQ. ID NO: 1805)
  - 5'-GGC CTC CBC CBG 3GB CBT G-3' (FRAG. NO:1201) (SEQ. ID NO:1210)
  - 5'-GTC CTT CTT GTC (CGC TGC C -3' (FRAG. NO:1202) (SEQ. ID NO:1211)
  - 5'-TCT CTG GGG TTT TCG GTC TGG GTG G-3 (FRAG. NO:1203) (SEQ. ID NO:1212)
- 5'-GCT TTC CTC CTG GGG CTG CTG CTG-3' (FRAG. NO:1204) (SEQ. ID NO:1213)
  - 5'-GGC TCT TCT TTT "GT TTC TGG CCT GGT G-3' (FRAG. NO:1205) (SEQ. ID NO:1214) 5'-CTC TCT CGT GCC CTT TCC-3' (FRAG. NO:1206) (SEQ. ID NO:1215)
  - 5'-CTT GGG TGT CTT GTT TTT GT-3' (FRAG. NO:1207) (SEQ. ID NO:1216
  - 5'-GGC CTC CBC CBG 3GB CBT G-3' (FRAG. NO:1208) (SEQ. ID NO:1217)
- 5'-CGGGBGTGGG GGTCCTGGBC GGCBCTGBBG GCBTCCBGGG CTCCCTTCCB GTCCTTCTTG TCCGCTGCCB GCBCCCCTTC BTTCCBGBGG CTGBTGGCCT CCBCCBGGGB CBTGBTTBGG TBGBBBCTBG GBGGCC-3' (FRAG. NO:1793) (SEQ. ID NC: 1806)

### Human Cathepsin G Nucleic Acid and Antisense Oligonucleotide Fragments

5'-CCCTCCBCBT CTGCTCTGBC CTGCTGGBCT CTGGBTCTGB BGBTBCGCCB TGTBGGGGCG GGBGTGGGGC



CTGCTCTCCC GGCCTCCGBT GBTCTCCCCT GCCTCBGCCC CBGTGGGTBG GBGBBBGGCC BGCBGBBGCB GGBGTGGCTG CBTCTTTCCT GGTGGGGCCT GCTCTCCCGG CCTCCGTGTG TTGCTGGGTG TTTTCCCGTC TCTGGTCTGC CTTCGGGGGT CGT-3' (FRAG. NO:1794) (SEQ. ID NO: 1807)

5'-GBBGBTBCGCC-3' (FRAG. NO:1795) (SEQ. ID NO: 1808)

5'-CBGCCCCBG-3' (F RAG. NO:1796) (SEQ. ID NO: 1809)

5'-TCC CGT CTC TGG-3' (FRAG. NO:1797) (SEQ. ID NO: 1810)

5'-GTG GGG CCT GCT CTC CCG GCC TCC G-3' (FRAG. NO:1209) (SEQ. ID NO:1218)

5'-TGT GTT GCT GG GIG TTT TCC CGT CTC TGG-3' (FRAG. NO:1210) (SEQ. ID NO:1219)

5'-TCT GCC TTC GGG GGT CGT-3' (FRAG. NO:1211) (SEQ. ID NO:1220)

10 5'-CCCTCCBCBT CTGCTCTGBC CTGCTGGBCT CTGGBTCTGB BGBTBCGCCB TGTBGGGGCG GGBGTGGGGC CTGCTCTCCC GGCC'TCCGBT GBTCTCCCCT GCCTCBGCCC CBGTGGGTBG GBGBBBGGCC BGCBGBBGCB GGBGTGGCTG-3' (I\*RAG. NO:1798) (SEQ. ID NO: 1811)

## Human Defensin 1 Nucleic Acid and Antisense Oligonucleotide Fragments

5'-CCGGGGCTGC BGCBBCCTCB TCBGCTCTTG CCTGGBGTGG CTCBGCCTGG GCCTGCBGGG CCBCCBGGBG BBTGGCBGCB BGGETGGCGB GGGTCCTCBT GGCTGGGGTC BCBGBTCCTC TBGCTBGGCB GGGTGBCCBG BGBGGGC GGG TCC 1CB TGG CTG GGG GCC TGG GCC TGC BGG GCC GCT CTT GCC TGG BGT GGC TC GCC CBG BGT CTT CCC TGG T GCTCAGCCTC CAAAGGAGCC AGCCTCTCCC CAGTTCCTGA AATCCTGAGT GTTGCCTGCC AGTCGCCATG AGAACTTCCT ACCTTCTGCT GTTTACTCTC TGCTTACTTT TGTCTGAGAT GGCCTCAGGT GGTAACTTTC TCACAGGCCT TGGCCACAGA TCTGATCATT ACAATTGCGT CAGCAGTGGA GGGCAATGTC 20 TCTATTCTGC CTGCCCGATC TTTACCAAAA TTCAAGGCAC CTGTTACAGA GGGAAGGCCA AGTGCTGCAA GTGAGCTGGG AGTGACCAGA AGAAATGACG CAGAAGTGAA ATGAACTTTT TATAAGCATT CTTTTAATAA AGGAAAATTG CTTTTGAAGT AT CTGCAGTGGT AAAAAGATTC TATATCTGCT GTTTGATGAA TGCAGCACCC ACTAGCCACA TAGTGCTCGT GAGCACTTGC AATGCGGCTA GGGTGATTTC AATTAACCTA AAAGAGAACA GCCACAGGGA GCATGTGGCT GCCATATTGG ATGGTGCTGC TTTGAGAACA AAATGAGAGA AATGAAGCCT CTATTTACCT TGGTTGGCGG AACACATTGA AGGGACTCTG TATTGATACC AGGCTTCAAA CTTTGGGAAG TGTACTGGCC AACTTAAACA CATCCACAGG AGAATGAAGA GGTTTGGGAA GGGACCAGAA ACCAGGCATT GAGGACAATG AGAAGAGTTT TTCAAAAGTG GAATTACTGC AAAAAGTGGA AAAATAGCCT TTGGATGGAA GTTACTGATG AGACAATTTC CATCGGTGTG AAAGCCATCT TTCCAACAGA GATCTGCAAC ATGAGAATGT ACTGTCTCCT AGGCTAGCGA TGGCCTCTTG TATTAGTCCG CTCAGGCTAC CAGATTTATC GTTTAAACTG CCCATAAACA GACC'AGGCAG TTTAAACAAC AGAAATTTAT TTCCTCGCAG TCCTGGAGGC AGGAAGTCTG CGATCAAGGT GGAAGCAGGG TTGGCTTCTT CTCAGGTGTC TGTCCTTGGC TGGTAGATGA CCGCCGCCTC CCTGGGTCCT CACATGGTCT TTCCTCTGTG TGTGTCTGTC CCAATCTCTT CTTATAAGGA TGCAAGTCTT ATGGATCAGA GCACACCCA ATGACCGTGT TTAACTTGAA TCACCTCTTT AAAGTTTCTC TCTCCAAATA CAATCACCTC CTGAGGCACT GTTAGGGCTT CGACACAGGA ATTCTTTTCC TAGGGGATTC AGTTCAGTCC AAAACGCCTA CCACTGGAGA CTTGCAACAT GGCGGCCTGC TGGTCCCTCG CCAGGAATAT CACAGGCGAC TGTTCCCTGT TGCATGGAAT AGAAGGCTAT TCCAGAGTAC TGTCTCTATT TATCAGATCT GGGATACTGG GAGAAGGGCA AAA AAAGTC CAAGTAGAAA AAAAAACTAT GAAAGTTTTA GAGAGTAACC ATAATTTCAG CCCGATGTGA AACCATCCTA GATTTCAGCT GAAATAGTGA TGTGGGAAGT GAGGGGGCCG GGATTCAAGG CAGAGGGAAC AGCCTAACTG AAGGCATGGA AGGAGGGAAG TGTAGGCTGT GTTTGAAGAG TGGCAGCTGC TTCCACATTT CTAAAACACA GGATGTGATT TTGGGGTGTG TTGAGACAAG GCAGAAAACT TGTTTGGAAA
AATAACTTGA ATTCCCTGCA CATTTAAAAT CTCTCAGCAG AAGAAAACCC CACTCAGAAC CCCACTGTTC
ATTCCTTGGC TTGTATTTGG SCACAGCTGG CATAGCCCCA GACTGAGTAA GCTCTTCAGA CACCTCATTT ATTTGTTCTG CTTTCGCGAG ATGTTCTCAA ATCGTTGCAG CTACAAGCCA TGAGTCTGAA GTGTTTGTGT TCCCTCCTTA CAGGTGGTAA CTTTCTCACA GGCCTTGGCC ACAGATCTGA TCATTACAAT TGCGTCAGCA GTGGAGGGCA ATGTCTCTAT TCTGCCTGCC CGATCTTTAC CAAAATTCAA GGCACCTGTT ACAGAGGGAA GGCCAAGTGC TGCAAGTGAG CTGAGAGTGA CCAGAAGAAA TGACGCAGAA GTGAAATGAA CTTTTTATAA GCATTCTTTT AATAAGGAA AATTGCTTTT GAAGTATACC TCCTTTGGGC CAAAATGAAT CTTGTGTCTC AATTGGAAGA GGTAAAGAAG TAGGGGGTTA GGGTGCATGG GTTGGAACGT GAGACAGGTC GAACCACAAA GCCTGCCTGG AAAAGGGGAG TGACGTCCTA GGCTTCAGTG ATGTCACCTC CACTTTGTTT GATCCACAAA CCAACAGGTG ACTGATTTTG GTCAGCTCAG CCTCCAAAGG AGCCAGCCTC TCCCCAGTTC CTGAAATCCT GAGTGTTGCC TGCCAGTCGC CATGAGAACT TCCTACCTTC TGCTGTTTAC TCTCTGCTTA CTTTTGTCTG AGATGGCCTC AGGTGGTAAC TTTCTCACAG GCCTTGGCCA CAGATCTGAT CATTACAATT GCGTCAGCAG TGGAGGGCAA TGTCTCTATT CTGCCTGCCC GATCTTTACC AAAATTCAAG GCACCTGTTA CAGAGGGAAG GCCAAGTGCT GCAAGTGAGC TGGGAGTGAC CAGAAGAAAT GACGCAGAAG TGAAATGAAC TT -3' (FRAG.NO:1799) (SEO. ID NO: 3010) 5'-GTCAGCTCAG CC'CCAAAGG AGCCAGCCTC TCCCCAGTTC CTGAAATCCT GAGTGTTGCC TGCCAGTCGC CATGAGAACT TCCIACCTTC TGCTGTTTAC TCTCTGCTTA CTTTTGTCTG AGATGGCCTC AGGTGGTAAC TTTCTCACAG GCCTIGGCCA CAGATCTGAT CATTACAATT GCGTCAGCAG TGGAGGGCAA TGTCTCTATT CTGCCTGCCC GATCITTACC AAAATTCAAG GCACCTGTTA CAGAGGGAAG GCCAAGTGCT GCAAGTGAGC

TGGGAGTGAC CAGAA.GAAAT GACGCAGAAG TGAAATGAAC TT-3' (FRAG.NO: ) (SEQ. ID NO: 2475)



5'-CTGCAGTGGT AAAAAGATTC TATATCTGCT GTTTGATGAA TGCAGCACCC ACTAGCCACA TAGTGCTCGT GAGCACTTGC AATCCGGCTA GGGTGATTTC AATTAACCTA AAAGAGAACA GCCACAGGGA GCATGTGGCT GCCATATTGG ATGCTGCTGC TTTGAGAACA AAATGAGAGA AATGAAGCCT CTATTTACCT TGGTTGGCGG AACACATTGA AGGGACTCTG TATTGATACC AGGCTTCAAA CTTTGGGAAG TGTACTGGCC AACTTAAACA CATCCACAGG AGA/.TGAAGA GGTTTGGGAA GGGACCAGAA ACCAGGCATT GAGGACAATG AGAAGAGTTT TTCAAAAGTG GAATTACTGC AAAAAGTGGA AAAATAGCCT TTGGATGGAA GTTACTGATG AGACAATTTC CATCGGTGTG AAAGCCATCT TTCCAACAGA GATCTGCAAC ATGAGAATGT ACTGTCTCCT AGGGTAGCGA TGGCCTCTTG TATTAGTCCG CTCAGGCTAC CAGATTTATC GTTTAAACTG CCCATAAACA GACCAGGCAG TTTAAACAAC AGAAATTTAT TTCCTCGCAG TCCTGGAGGC AGGAAGTCTG CGATCAAGGT GGAAGCAGGG TTGGCTTCTT CTCAGGTGTC TGTCCTTGGC TGGTAGATGA CCGCCGCCTC CCTGGGTCCT CACATGGTCT TTCCTCTGTG TGTGTCTGTC CCAATCTCTT CTTATAAGGA TGCAAGTCTT ATGGATCAGA GCACACCCCA
ATGACCGTGT TTAA.CTTGAA TCACCTCTTT AAAGTTTTCC TCTCCAAATA CAATCACCTC CTGAGGCACT
GTTAGGGCTT CGAC'ACAGGA ATTCTTTCC TAGGGGATTC AGTTCAGTCC AAAACGCCTA CCAGTGGAGA CTTGCAACAT GGCGGCCTGC TGGTCCCTCG CCAGGAATAT CACAGGCGAC TGTTCCCTGT TGCATGGAAT AGAAGGCTAT TCCAGAGTAC TGTCTCTATT TATCAGATCT GGGATACTGG GAGAAGGGCA AAATAAAGTC 15 CAAGTAGAAA AAAAAACTAT GAAAGTTTTA GAGAGTAACC ATAATTTCAG CCCGATGTGA AACGATCCTA GATTTCAGCT GAAATAGTGA TGTGGGAAGT GAGGGGGCCG GGATTCAAGG CAGAGGGAAC AGCGTAACTG AAGGCATGGA AGGAGGGAAG TGTAGGCTGT GTTTGAAGAG TGGCAGCTGC TTCCACATTT CTAAAACACA GGATGTGATT TTGCGGTGTG TTGAGACAAG GCAGAAAACT TGTTTGGAAA AATAACTTGA ATTCCCTGCA CATTTAAAAT CTCTCAGCAG AAGAAAACCC CACTCAGAAC CCCACTGTTC ATTCCTTGGC TTGTATTTGG SCACAGCTGG CATAGCCCCA GACTGAGTAA GCTCTTCAGA CACCTCATTT CATGAGTAGC CCCAAAGATC AATCATGGGC CAA'TTCTTG GAAGAAGA CTCTCCGGTG TTTTGCAGTT ATTTGTTCTG CTTTCGCGAG ATGTTCTCAA ATCCTTGCAG CTACAAGCCA TGAGTCTGAA GTGTTTGTGT TCCCTCCTTA CAGGTGGTAA CTTTCTCACA GGCCTTGGCC ACAGATCTGA TCATTACAAT TGCGTCAGCA GTGGAGGGCA ATGTCTCTAT TCTGCCTGCC CGATCTTTAC CAAAATTCAA GGCACCTGTT ACAGAGGGAA GGCCAAGTGC TGCAAGTGAG CTGAGAGTGA CCAGAAGAAA TGACGCAGAA GTGAAATGAA CTTTTTATAA GCATTCTTTT AATAAAGGAA AATTGCTTTT GAAGTATACC TCCTTTGGGC CAAAATGAAT CTTGTGTCTC AATTGGAAGA GGTAAAGAAG TAGGGGGTTA GGGTGCATGG GTTGGAACGT GAGACAGGTC GAACCACAAA GCCTGCCTGG AAAAGGGGAG TGACGTCCTA GGCTTCAGTG ATGTCACCTC CACTTTGTTT GATCCACAAA CCAACAGGTG ACTGATTTTG-3' (FRAG.NO: ) (SEQ. ID NO: 2474) 5'-GCTCAGCCTC CA.\AGGAGCC AGCCTCTCCC CAGTTCCTGA AATCCTGAGT GTTGCCTGCC AGTCGCCATG AGAACTTCCT ACCITCTGCT GTTTACTCTC TGCTTACTTT TGTCTGAGAT GGCCTCAGGT GGTAACTTTC TCACAGGCCT TGG('CACAGA TCTGATCATT ACAATTGCGT CAGCAGTGGA GGGCAATGTC TCTATTCTGC CTGCCCGATC TTTACCAAAA TTCAAGGCAC CTGTTACAGA GGGAAGGCCA AGTGCTGCAA GTGAGCTGGG AGTGACCAGA AGANATGACG CAGAAGTGAA ATGAACTTTT TATAAGCATT CTTTTAATAA AGGAAAATTG CTTTTGAAGT AT-3' (IFRAG.NO:\_\_\_) (SEQ. ID NO: 2472) 5'-CCGGGGC-3' (FRACLNO:1800) (SEQ. ID NO: 1813) 5'-GG GCCTGCBGGG CC-3' (FRAG.NO:1801) (SEQ. ID NO: 1814) 5'-GGCBGCB BGG-3' (J'RAG.NO:1802) (SEQ. ID NO: 1815) 5'-GGG TCC TCB TGG CTG GGG-3' (FRAG. NO:1212) (SEQ. ID NO:1221) 5'-GCC TGG GCC TGC BGG GCC-3' (FRAG. NO:1213) (SEQ. ID NO:1222) 5'-GCT CTT GCC TGG 3GT GGC TC-3' (FRAG. NO:1214) (SEQ. ID NO:1223) 5'-GCC CBG BGT CTT CCC TGG T-3' (FRAG. NO:1215) (SEQ. ID NO:1224)

5'-CCGGGGCTGC BGCBBCCTCB TCBGCTCTTG CCTGGBGTGG CTCBGCCTGG GCCTGCBGGG CCBCCBGGBG BBTGGCBGCB BGGI:TGGCGB GGGTCCTCBT GGCTGGGGTC BCBGBTCCTC TBGCTBGGCB GGGTGBCCBG BGBGGGC-3' (FRAG.NO:1803) (SEQ. ID NO: 1816)

#### Human Defensin 2 Nucelic Acid and Antisense Oligonucleotide Fragments

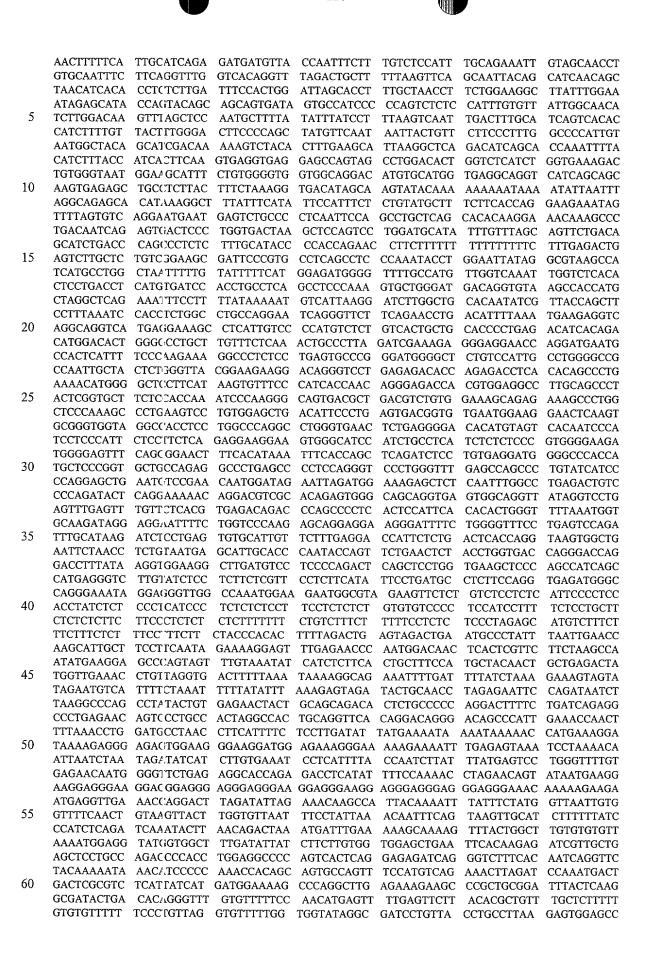
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	A COMPONIO A	CAACCTCACA	TTTTTAAATICA	1010000100	O LOTTO LTO L	COLL LOCOTO	, mmamagaa
					CAGTTCATGA		ATTGTCCCCA
	TGTCTCTGTC	ACTGCTGCAC		TCACAGACAT	GGACACTGGG	GCCTGCTTGT	TTCTCAAACT
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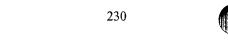


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GCACTCAGTC TCAC'CTGGGT GTTCTCCAAC ATCCCAGCTC AGCCAAATGG CTTTCATTAG TTTTTATGGT
TAGACCCCAG GTCCTCGGGA CACTGCTTTA GAAACACATT CCAAATCCTC CTCTGTGTC AGGTGGCATT
CCTATCCCAA TCTCITTGCA GGGCGTATAC TGTGATACGC AGCCAGGCTG TCCCAGAGGC CTTAAATATT CCCTTGGTGC AGGTAGTTCA GCTTAGCCAC AGCCAATGCA TCACAGGGTC AACTGTGTTA GGAGCCATTG AGAATCCATA GTTCGTTGCT GCCTGGGCCT GGCCAGGGCT GACCAAGGTA GATGAGAGGT TCCTCTGTGG AGTTCTACTT TAACCTCACC TTCCCACCAA ATTTCTCAAC TGTCCTTGCC ACCACAATTA TTTAATGGAC CCAACAGAAA GTA/CCCCGG AAATTAGGAC ACCTCATCCC AAAAGACCTT TAAATAGGGG AAGTCCACTT GTGCACGGCT GCTCCTTGCT ATAGAAGACC TGGGACAGAG GACTGCTGTC TGCCCTCTCT GGTCACCCTG CCTAGCTAGA GGATCTGTAA GTACTACAAA ACTTAAACTT TACACTGAGT TTTCATCATT GAAGCTATGC CTCCAATCTG ACCTCTGACT GTGGGGCCGC CCCAGAGGGA CCCAGCGGGT GAATCCCTGC TAGGAACGTC TGTCCGGACC TCTGGTGACT GCTGGGGACG ATGGCTTCCA GCTAACTTAA TAGAGAAACT CAAGCAGTTT CCTTCTAAAT ACACATGTCA CATGTCCTGG TTGACATGTC CAGTAAGAAG ACTATCACAG GTCTTTGGAA CATTCTTTTG AGAC AAACCT ATTTAGGTCC TTGGTCTGTT TTTCAATCAG GTTGTTTGAT TTTTGCTATT GAGTTGTTGG AATI'CCTTAT GTATTCAGAT ATTTGCCCCT TCTGCCATGT AGGTTTTGCA AATATTTTCT CTCATTTCT GGGTTATCTT TTCACTCGGT TGATTGTTTC CTTTGCTGTG CAGATGCTTT AGCGTTAAAT GAAGCCACAC TTG: CTATTT TCCCTTTTAT TGCCTGTGCC TTTGGTGTCA TAGCCAAGAA ATCATTACCT ACATCAATGT CAAAAGCTTT ATCCTTCTAT ACACTTCTAG TAGTTTATGG TTTCAGTTGT TACATTTAGG TTTTCAATTC ATTCIGAGTT GATGTTCCTA CATGGTGTGA GATAAAGATT TAAATACATA CATATATAAA ATCATGAGGT AGTCTACACT ATAAATATAC AATTGTTAAT TGTTACTCAA GTCTAAGTAG AGGTGGAAAT AATAAACTTT CTTTTTTTA CTTAAACCAC TCTGTGTCAC TGAGCTGATT TCACCTTTAG CCTGATAAAA TCATTGTCCT CTCCACCTG ATTCCTACAG GAGACTACTC ACCCCATAAC CTCAAAAAACC TCTTCATGAG GATGGTAAGT CACCTGAATC CTGAAGTGAA TTACTCGCTA TTCCATTGGA ACTCATATAG GACACCAGAA TCTAGACCTC CAGAGAACAG CAGGACCCAT CTTCAGAAAA TAAGAAGCAT TTGTTCCCTG AGCCTGTTGA ATCAAAGTGC AATITCTATT CTTTTTGGAA TGTTAAAAAG TGAATCATAA TATTTAAGCA GGTGAACCCA CGAGTAACAT AGCAGGGTCT TTCTTGTCAT TATTAGCTCC AACCTAGCAC AGACATTAAA GGTACAGATG TATACTAGCA TGAAACTGGG AGAACAGGAG CATTCGAGCA ACCTTGAGAC CAATGGGCCT CTCTTATAAA ATGCACACCT CCTCTCACTG AGATTGAGGA AGGTTTCTTG TCTCCGAGCC TTCTCCCAGT AGAGCTATAA ATCCAGGCTG GCTC'CTCCCT CCCCACACAG CTGCTCCTGC TCTCCCTCCT CCAGGTGACC CCAGCCATGA GGACCCTCGC CATCCTTGCT GCCATTCTCC TGGTGGCCCT GCAGGCCCAG GCTGAGCCAC TCCAGGCAAG AGCTGATGAG GTTC CTGCAG CCCCGGAGCA GATTGCAGCG GACATCCCAG AAGTGGTTGT TTCCCTTGCA TGGGACGAAA GCTIGGCTCC AAAGCATCCA GGTGAGAGAG GCAGGCATGC AGAGCTGCTA AGTCTAGAGG GAAGGACGGG AGAGAGTTC CAGAGTTGGG TCTCAGCAGT CTATGTCACT GAGGTGGCTT CACTTAGAAT CTCTGGGCAT TGATTTCTC ATCTAGAAAT TGAACAGAGA GCCAAATAAA CCTGAGAAAC TTTATTTCTC CAAAGACTTG ATTCCAAGAA ACATCTGTGA AATTCACTAA GTTTAAGATA TGAAGAGACA GACTAGTTAT TTCTGGATCT AAACAAGTAG ACTTAGTTGT AAAGAGAACA TTTTACTCTA TCTACAGAAG AGCTTTTAAA AACTGCAGCC AAGCCTGAGG GTAAGTTCAG GTGTGTGTGT GATGGGGCAG GAATGCAAAA ATGAGAGCAA AGGAGAATGA GTC CAAATT CTGTGTGACA AGCACTGCTC TGCGTGTTTA TTCCTATCGA CTGAGGTTGT TCGTGCTACC GGCIGCAATG CAGCCAGCAT CACCTGTCAG CTAGCATGTG ACTTCCCCGA GATTCTTTTT CTTACCCACT GCTAACTCCA TACTCAATTT CTCATGCTCT CCCTGTCCCA GGCTCAAGGA AAAACATGGA CTGCTATTGC AGAATACCAG CGTGCATTGC AGGAGAACGT CGCTATGGAA CCTGCATCTA CCAGGGAAGA CTCTGGGCAT TCTGCTGCTG AGCTTGCAGA AAAAGAAAAA TGAGCTCAAA ATTTGCTTTG AGAGCTACAG GGAATTGCTA TTACTCCTGT ACCTTCTGCT CAATTTCCTT TCCTCATCTC AAATAAATGC CTTGTTACAA GATTTCTGTG TTTCCACCTC TTTAATGTGT GATATGTGTC TGTGTCAAGA CACTTGGGAT ACACGTACCA



AAACGCAAAA TCAAATTTTT GAACAATATA-3' (FRAG. NO: ) (SEQ. ID NO:3012)

## Human Defensin 3 Nucleic Acid and Antisense Oligonucleotide Fragments

5'-CGCTGCBBTC TGCTCCGGGG CTGCBGCBBC CTCBTCBGCTC TTGCCTGGBGTG GCTCBGCCTGG GCCTGCBGGG CCBCCBGGBGB BTGCCBGCBBG GBTGGCGBGGG TCCTCBTGGC TGGGGTCBCCT GGBGGBGGGB GBGCBGGGG TCCTCBTGGC TGGGGTCCCT CTCTCCCGTC CT CCTACCTTGC TATAGAAGAC CTGGGACAGA GGACTGCTGT CTGCCCTCTC TGGTCACCCT GCCTAGCTAG AGGATCTGTG ACCCCAGCCA TGAGGACCCT CGCCATCCTT GCTGCCATTC TCCT3GTGGC CCTGCAGGCC CAGGCTGAGC CACTCCAGGC AAGAGCTGAT GAGGTTGCTG CAGCCCCGGA GCAGATTGCA GCGGACATCC CAGAAGTGGT TGTTTCCCTT GCATGGGACG AAAGCTTGGC TCCAAAGCAT CCAGGCTCAA GGAAAAACAT GGACTGCTAT TGCAGAATAC CAGCGTGCAT TGCAGGAGAA CGTCGCTATG GAACCTGCAT CTACCAGGGA AGACTCTGGG CATTCTGCTG CTGAGCTTGC AGAAAAAGAA AAATGAGCTC AAAA' TTGCT TTGAGAGCTA CAGGGAATTG CTATTACTCC TGTACCTTCT GCTCAATTTC CTTT-3' (FRAG. NO:1804) (SEQ. ID NO:3013) 5'-CCTACCTTGC TAT'AGAAGAC CTGGGACAGA GGACTGCTGT CTGCCCTCTC TGGTCACCCT GCCTAGCTAG AGGATCTGTG ACCC'CAGCCA TGAGGACCCT CGCCATCCTT GCTGCCATTC TCCTGGTGGC CCTGCAGGCC CAGGCTGAGC CACTCCAGGC AAGAGCTGAT GAGGTTGCTG CAGCCCCGGA GCAGATTGCA GCGGACATCC CAGAAGTGGT TGTTTCCCTT GCATGGGACG AAAGCTTGGC TCCAAAGCAT CCAGGCTCAA GGAAAAACAT GGACTGCTAT TGCAGAATAC CAGCGTGCAT TGCAGGAGAA CGTCGCTATG GAACCTGCAT CTACCAGGGA AGACTCTGGG CATICTGCTG CTGAGCTTGC AGAAAAAGAA AAATGAGCTC AAAATTTGCT TTGAGAGCTA CAGGGAATTG CTATTACTCC TGTACCTTCT GCTCAATTTC CTTT-3' (FRAG. NO:\_\_\_) (SEQ. ID NO:2478)
5'-GAATTCCCTG TAAGCCCTGT TACAGGGGCT GCACCCCAGA TACAACCTGA CCTGTGTCCA AGGCGGGCAA CTCAACCCTT AGATATTGAA TGGGTCCCAT GGCACCAATG CTTAAACACC AGCAGCCCTC ACAACCACAG ATCGTGTTTT AAGGATGAGG AGGTAGTTCT CTGGATGCAC AGGCTTCAAT CCAAATGGGC TCATGACGCC GCAGCACACA CCCAGTCTGC AGCCTGAAGA GTTGGAGCAT TGCATTCACA GAAAGCATCC AGACATGATC ATGGGCTCAG GGATACACCT GTTCTCCGAT GTGTACCAGT GAAGGATGGA AACTCCTATG CCTCCCAGAA AGCACCACTC AAGCTTTTGC TGAATGCTTC TCTGAAGGCC CACAAGGCTG AGAGGCTGTG CAACACCAGC AGTAAAGTGA ATGCCCAGAC TCCCACCTCC TTTCTTGGGT GGCCATCTGG AAAGGCCACT CCCACCCTGA TGGCTAATGC CTCAGACCAG TTCTTGGCCC AGATGATCCT AGACAATTGT TTAAGCTTAA ACTGTTCATT GGCCAAGCAA ACAGGTGATA GTACCTCTGG GGAACCACAT GCCGCGTGTA CATCCAGATC TCAGGAGAAC CCAAAAATGT CTGTTCCACA TAGCAACAGA AGCCCAGGTA GCACTCAGTC TCACCTGGGT GTTCTCCAAC ATCCCAGCTC AGCC'AAATGG CTTTCATTAG TTTTTATGGT TAGACCCCAG GTCCTCGGGA CACTGCTTTA GAAACACATT CCAAATCCTC CTCTGTGTC AGGTGGCATT CCTATCCCAA TCTCTTTGCA GGGCGTATAC TGTGATACGC AGCC'AGGCTG TCCCAGAGGC CTTAAATATT CCCTTGGTGC AGGTAGTTCA GCTTAGCCAC AGCCAATGCA TCACAGGGTC AACTGTGTTA GGAGCCATTG AGAATCCATA GTTGGTTGCT GCCTGGGCCT GGCCAGGGCT GACCAAGGTA GATGAGAGGT TCCTCTGTGG AGTTCTACTT TAACCTCACC TTCCCACCAA ATTTCTCAAC TGTCCTTGCC ACCACAATTA TTTAATGGAC CCAACAGAAA GTAACCCCGG AAATTAGGAC ACCTCATCCC AAAA GACCTT TAAATAGGGG AAGTCCACTT GTGCACGGCT GCTCCTTGCT ATAGAAGACC
TGGGACAGAG GACTGCTGC TGCCCTCTCT GGTCACCCTG CCTAGCTAGA GGATCTGTAA GTACTACAAA
ACTTAAACTT TACACTGAGT TTTCATCATT GAAGCTATGC CTCCAATCTG ACCTCTGACT GTGGGGCCGC
CCCAGAGGGA CCCAGCGGGT GAATCCCTGC TAGGAACGTC TGTCCGGACC TCTGGTGACT GCTGGGGACG
ATGGCTTCCA GCTAACTTAA TAGAGAAACT CAAGCAGTTT CCTTCTAAAT ACACATGTCA CATGTCCTGG
TTGACATGTC CAGTAAGAAG ACTATCACAG GTCTTTGGAA CATTCTTTTG AGAGAAACCT ATTTAGGTCC 40 TTGGTCTGTT TTTCAATCAG GTTGTTTGAT TTTTGCTATT GAGTTGTTGG AATTCCTTAT GTATTCAGAT ATTTGCCCCT TCTGCCATGT AGGTTTTGCA AATATTTTCT CTCATTTTCT GGGTTATCTT TTCACTCGGT TGATTGTTTC CTTTGCTGTG CAGATGCTTT AGCGTTAAAT GAAGCCACAC TTGTCTATTT TCCCTTTTAT TGCCTGTGCC TTTGGTGTCA TAGCCAAGAA ATCATTACCT ACATCAATGT CAAAAGCTTT ATCCTTCTAT ACACTTCTAG TAGTTATGG TTTCAGTTGT TACATTTAGG TTTTCAATTC ATTCTGAGTT GATGTTCCTA CATGGTGTGA GATA.AAGATT TAAATACATA CATATATAAA ATCATGAGGT AGTGTACACT ATAAATATAC AATTGTTAAT TGTTACTCAA GTCTAAGTAG AGGTGGAAAT AATAAACTTT CTTTTTTTA CTTAAACCAC TCTGTGTCAC TGAC:CTGATT TCACCTTTAG CCTGATAAAA TCATTGTCCT CTCCACCCTG ATTCCTACAG GAGACTACTC ACCC'CATAAC CTCAAAAACC TCTTCATGAG GATGGTAAGT CACCTGAATC CTGAAGTGAA TTACTCGCTA TTCCATTGGA ACTCATATAG GACACCAGAA TCTAGACCTC CAGAGAACAG CAGGACCCAT CTTCAGAAAA TAAGAAGCAT TTGTTCCCTG AGCCTGTTGA ATCAAAGTGC AATTTCTATT CTTTTTGGAA TGTTAAAAAG TGA/TCATAA TATTTAAGCA GGTGAACCCA CGAGTAACAT AGCAGGGTCT TTCTTGTCAT TATTAGCTCC AACCTAGCAC AGACATTAAA GGTACAGATG TATACTAGCA TGAAACTGGG AGAACAGGAG CATTCGAGCA ACCITGAGAC CAATGGGCCT CTCTTATAAA ATGCACACCT CCTCTCACTG AGATTGAGGA AGGTTTCTTG TCTCCGAGCC TTCTCCCAGT AGAGCTATAA ATCCAGGCTG GCTCCTCCCT CCCCACACAG CTGCTCCTGC TCTCCCTCCT CCAGGTGACC CCAGCCATGA GGACCCTCGC CATCCTTGCT GCCATTCTCC TGGTGGCCCT GCACGCCCAG GCTGAGCCAC TCCAGGCAAG AGCTGATGAG GTTGCTGCAG CCCCGGAGCA GATTGCAGCG GACATCCCAG AAGTGGTTGT TTCCCTTGCA TGGGACGAAA GCTTGGCTCC AAAGCATCCA

GGTGAGAGAG GCAGGCATGC AGAGCTGCTA AGTCTAGAGG GAAGGACGGG AGAGAGGTTC CAGAGTTGGG



TCTCAGCAGT CTATGTCACT GAGGTGGCTT CACTTAGAAT CTCTGGGCAT TGATTTCTC ATCTAGAAAT TGAACAGAGA GCCAAATAAA CCTGAGAAAC TTTATTTCTC CAAAGACTTG ATTCCAAGAA ACATCTGTGA AATTCACTAA GTTTAAGATA TGAAGAGACA GACTAGTTAT TTCTGGATCT AAACAAGTAG ACTTAGTTGT AAAGAGAACA TTTTACTCTA TCTACAGAAG AGCTTTTAAA AACTGCAGCC AAGCCTGAGG GTAAGTTCAG GTGTGTGTGT GATGGGGCAG GAATGCAAAA ATGAGAGCAA AGGAGAATGA GTCTCAAATT CTGTGTGACA AGCACTGCTC TGCCTGTTA TTCCTATCGA CTGAGGTTGT TCGTGCTACC GGCTGCAATG CACCTGTCAG CTACCAGTG ACTTCCCGA GATTCTTTTT CTTACCACCT GCTAACTCCA TACTCAATTT CTCATGCTCT CCCT-3TCCCA GGCTCAAGGA AAAACATGGA CTCTGGGCAT TCTGCTGCTG AGCTTGCAGA AAAAGAAAAA TGA-3CTCAAA ATTTGCTTTG AGAGCTACAG GGAATTGCTA TTCCTCTGCT CAATTTCCTGCT TCCTCATCT AAATAAATGC CTTGTTACAA GATTTCTGTG TTTCCACCTC TTTAATGTGT GATATTCCTT TCCTCATCTC AAATAAATGC CTTGTTACAA GATTTCTGTG TTTCCACCTC TTTAATGTGT GATATGTGT TGTGTCAAGA CACTTGGGAT ACACGTACCA AAACGCAAAA TCAAATTTTT GAACAATATA-3' (FRAG. NO:\_\_) (SEQ. ID NO:2477)

5'-GGCBGCBBGG-3' (FRAG. NO:1805) (SEQ. ID NO:1818)

- 15 5'-GG CTG GGG-3' (FRAG. NO:1806) (SEQ. ID NO:1819)
  - 5'-GGGGTCBCC-3' (FRAG. NO:1807) (SEQ. ID NO:1820)
  - 5'-GGG TCC TCB TGG CTG GGG TC-3' (FRAG. NO:1216) (SEQ. ID NO:1225)
  - 5'-CCT CTC TCC CGT CCT-3' (FRAG. NO:1217) (SEQ. ID NO:1226)
- 5'-CGCTGCBBTC TGC1CCGGGG CTGCBGCBBC CTCBTCBGCTC TTGCCTGGBGTG GCTCBGCCTGG GCCTGCBGGG

  CCBCCBGGBGB BTGGCBGCBBG GBTGGCGBGGG TCCTCBTGGC TGGGGTCBCCT GGBGGBGGGB GBGCBGG-3'

  (FRAG. NO:1808) (SE(). ID NO:1821)

## Human Macrophage Inflammatory Protein-1-alpha/RANTES Receptor Nucleic Acid and Antisense Oligonucleotide Fragments

- 5'-GTCTTTGTTT CTCGGCTCGT GCCCCBTCCC GGCTTCTCC TGGTTCCGTC CTCTGTGGTG TTTGGCCCTG

  CTTCCTTTTG CCTGTTGAGG GGGCAGCAGT TGGGCCCCAA AGGCCCTCTC GTTCACCTTC TGGCACGGAGTT
  GCATCCCCATA GTCAAACTCT GTGGTCGTGT CATAGTCCTC TGTGGTGTTT GGAGTTTCCA TCCCGGCTTC
  TCTCTGGTTC CAACGGAGB GGGGGCBGCB GTTGGGCCCC BBBGGCCCTC TCGTTCBCCT TCTGGCBCGG
  BGTTGCBTCC CCBTBGTCBB BCTCTGTGGT CGTGTCBTBG TCCTCTGTGG TGTTTGGBGT TTCCBTCCCG
  GCTTCTCTCT GGTTC\'DBGG GB-3' (FRAG. NO:1809) (SEQ. ID NO:1822)
- 30 5'-GGGCC CC-3' (FRAG. NO:1810) (SEQ. ID NO:1823)
  5'-GGGGGCBGC-3' (I'RAG. NO:1811) (SEQ. ID NO:1824)
  5'-CCCGGCTTC-3' (FRAG. NO:1812) (SEQ. ID NO:1825)
  5'-GTC TTT GTT TCT GGG CTC GTG CC-3' (FRAG. NO:1218) (SEQ. ID NO:1227)
  5'-CCB TCC CGG CTT (TC TCT GGT TCC-3' (FRAG. NO:1219) (SEQ. ID NO:1228)
- 5'-GTC CTCTGT GGT (itt tgg-3' (frag. No:1220) (seq. id no:1229)
  5'-CCC tgc ttc ctt 'tg cct gtt-3' (frag. no:1221) (seq. id no:1230)
  5'-GAGGGGGCAG CAGTTGGGCC CCAAAGGCCC tctcgttcac cttctggcac ggagttgcat ccccatagtc AAACTCTGTG gtcgt-3' (frag. no:1222) (seq. id no:1231)
- 5'-GTCATAGTCCTCTCTGGTGTTTGGAGTTTCCATCCCGGCTTCTCTCTGGTTCCAAGGGA-3' (FRAG.NO:1223)(SEQ.ID NO:1232)
  - 5'-GBGGGGGCBG CB3TTGGGCC CCBBBGGCCC TCTCGTTCBC CTTCTGGCBC GGBGTTGCBT CCCCBTBGTC BBBCTCTGTG GTCGT'3-3' (FRAG. NO:1224) (SEQ. ID NO:1233)
  - 5'-TCBTBGTCCTCTGT'3GTGTTTGGBGTTTCCBTCCCGGCTTCTCTCTGGTTCCBBGGGB-3'(FRAG. NO:1225)(SEQ. ID NO:1234)

## 45 **RANTES Antisense Oligonucleotide Fragments**

50 TGTTCCTCCC TTCCT GCCT CT-3' (FRAG. NO: 1813) (SEQ. ID NO: 1826)

- 5'-GGGTTGGC-3' (FRAG. NO: 1814) (SEQ. ID NO: 1827)
- 5'-CGGGG CBG-3' (FRAG. NO: 1815) (SEQ. ID NO: 1828)
- 5'-CCCGGGTTCG-3' (I'RAG. NO: 1816) (SEQ. ID NO: 1829)
- 5'-GGGTGTGGTG-3' (I'RAG. NO: 1817) (SEQ. ID NO: 1830)
- 55 5'-GGGCBCGGGG CB3TGGGCGG GCBBTGTBGG CBBBGCBGCB GGGTGTGGTG TCCGBGGBBT BTGGGGBGGC BGBTGCBGGB GCGC-2' (FRAG. NO:1226) (SEQ. ID NO:1235)
  5'-BGBGGGCBGTB GCBBTGBGGB TGBCBGCGBG GCGTGCCGCG GBGBCCTTCB TGGTBCCTGT GGBGBGGCTG TCGGBGG-3' (FRAG. NO:1227) (SEQ. ID NO:1236)
- 60 NO:1228) (SEQ. ID NC:1237)



NO:1229) (SEQ. ID NC:1238)

- 5'-GGGTGTGGTGTCC(i-3' (FRAG. NO:1230) (SEQ. ID NO:1239)
- 5'-CTTGGCGGTTCTTTCGGGTG-3' (FRAG. NO:1231) (SEQ. ID NO:1240)
- 5'-TTTCTTCTCTGGGTTGGC-3' (FRAG. NO:1232) (SEQ. ID NO:1241)
  5'-CTGCTGCTCGTCGTGGTC-3' (FRAG. NO:1233) (SEQ. ID NO:1242)
  5'-GCTCCGCTCCCGGC(TTC-3' (FRAG. NO:1234) (SEQ. ID NO:1243)
  5'-GTCTCGCTCTGTCGCCC-3' (FRAG. NO:1235) (SEQ. ID NO:1244)
  - 5'-CTTCCTTCTTGTC 3' (FRAG. NO:1236) (SEQ. ID NO:1245)
- 5'-GTGTTCCTCCCTTCCTTGCCTCT-3' (FRAG. NO:1237) (SEQ. ID NO:1246)
  - 5'-GGCBCGGGG CB'TGGGCGG GCBBTGTBGG CBBBGCBGCB GGGTGTGGTG TCCGBGGBBT BTGGGGBGGC BGBTGCBGGB GCGCBGBGGG CBGTBGCBBT GBGGBTGBCB GCGBGGCGTG CCGCGGBGBC CTTCBTGGTB CCTGTGGBGB GGCTGTCGGB GG-3' (FRAG. NO:1818) (SEO. ID NO:1831)

#### Human Muscarinic Acetylcholine Receptor HM1\* Nucleic Acid and Antisense Oligonucleotide Fragments

- 15 5'-GCTGCCCGGC GG'3GTGTGCG CTTGGCGCTC CCGTGCTCGG TTCTCTGTCT CCCGGTCCCC CTTGCCTGGC GTCTCGGGCC TTCGTCCTCT TCCTCTTCTT CCTTCCGCTC CGTGGGGGGCT GCTTGGTGGG GGCCTGTGCCT CGGGGTCCCG GGGCITCTGG CCCTTGCCGT TCATGGTGGC TAGGTGGGGC GTTCBTGGTG GCTBGGTGGG GC-3'(FRAG. NO:1819)(SEQ. ID NO: 1832)
  - 5'-GGTGGGGC-3' (FRAG. NO:1820) (SEQ. ID NO: 1833)
- 5'-GCCCGGCGGGG-3' FRAG. NO:1821) (SEQ. ID NO: 1834)
  - 5'-CGG GGC TTC TGG CCC-3' (FRAG. NO:1822) (SEQ. ID NO: 1835)
  - 5'-GTT CBT GGT GGC TBG GTG GGG C-3' (FRAG. NO:1238) (SEQ. ID NO:1247)
  - 5'-GCT GCC CGG CGG GGT GTG CGC TTG GC-3' (FRAG. NO:1239) (SEQ. ID NO:1248)
  - 5'-GCT CCC GTG CTC 3GT TCT CTG TCT CCC GGT-3' (FRAG. NO:1240) (SEQ. ID NO:1249)
- 5'-CCC CCT TTG CCT GGC GTC TCG G-3' (FRAG. NO:1241) (SEQ. ID NO:1250)
  - 5'-GCC TTC GTC CTC TTC CTC TTC CTT CC-3' (FRAG. NO:1242) (SEO. ID NO:1251)
  - 5'-GCT CCG TGG GGG CTG CTT GGT GGG GGC CTG TGC CTC GGG GTC C-3' (FRAG. NO:1243) (SEO. ID NO:1252)
  - 5'-CGG GGC TTC TGG CCC TTG CC-3' (FRAG. NO:1244) (SEQ. ID NO:1253)
  - 5'-GTT CAT GGT GGC TAG GTG GGG C-3' (FRAG. NO: 1245) (SEQ. ID NO:1254)

#### Human Muscarinic Acetylcholine Receptor HM3\* Nucleic Acid and Antisense Oligonucleotide Fragments

5'-GGG GTG GGT BGG CCG TGT CTG GGGGTT GGC CBT GTT GGT TGC CTCT TGG TGC TGC GCC GGG CGCG TCT GGG GCT TCT TGGC3 CTG GCG GGG GGG CCT CCTGCT CTG TGG CTG GGC GTT CCT TGG TGT TCT GGG TGGTGG CGG GCG TCG TGG CCT CTG TGGGGG CCC GCG GCT GCB GGG GTTG CCT GTC TGC TTC GTCCTT TGC

- GCT CCC GGG CCG C'GGG GTG GGT AGG CCG TGT CTG GGGGTT GGC CAT GTT GGT TGC CGGG CCC GCG GCT GCA GGG G-3' (FRAG. NO:1823) (SEO. ID NO:1836)
  - 5'-CCC GGG CGG-3' (FRAG. NO:1824) (SEQ. ID NO:1837)
  - 5'-G GCG GGG GGG CC-3' (FRAG. NO:1825) (SEQ. ID NO:1838)
  - 5'-CCC GGG CCG CC-3' (FRAG. NO: 1826) (SEQ. ID NO: 1839)
- 5'-GG CCG TGT-3' (F RAG. NO:1827) (SEQ. ID NO:1840)
  - 5'-GGG GTG GGT BGG CCG TGT CTG GGG-3' (FRAG. NO:1246) (SEQ. ID NO:1255)
  - 5'-GTT GGC CBT GTT GGT TGC C-3' (FRAG. NO:1247) (SEQ. ID NO:1256)
  - 5'-TCT TGG TGG TGC GCC GGG C-3' (FRAG. NO:1248) (SEQ. ID NO:1257)
  - 5'-GCG TCT TGG CT' TCT TCT CCT TCG GGC CCT CGG GCC GGT GCT TGT GG-3'(FRAG.NO:1249)(SEQ.ID
- NO:1258)

  - 5'-GCG CTG GCG GGG GGG CCT CCT CC-3' (FRAG. NO:1251) (SEQ. ID NO:1260)
  - 5'-GCT CTG TGG CTG GGC GTT CCT TGG TGT TCT GGG TGG C-3' (FRAG. NO:1252) (SEQ. ID NO:1261)
  - 5'-TGG CGG GCG TGG TGG CCT CTG TGG TGG-3' (FRAG. NO:1253) (SEQ. ID NO:1262)
- 5'-GGG CCC GCG GCT GCB GGG G-3' (FRAG. NO:1254) (SEQ. ID NO:1263)
  - 5'-TTG CCT GTC TGC 'TTC GTC-3' (FRAG. NO:1255) (SEQ. ID NO:1264)
  - 5'-CTT TGC GCT CCC GGG CCG CC-3' (FRAG. NO:1256) (SEQ. ID NO:1265)
  - 5'-GGG GTG GGT AGC CCG TGT CTG GGG-3' (FRAG. NO:1257) (SEO. ID NO:1266)
  - 5'-GTT GGC CAT GTT GGT TGC C-3' (FRAG. NO:1258) (SEQ. ID NO:1267)
- 5'-GGG CCC GCG GCT GCA GGG G-3' (FRAG. NO:1259) (SEO. ID NO:1268)

## Human Fibronectin\* Antisense Oligonucleotide Fragments

GGC GTC GG CCG CTC GCG CCT GGG GTT CCC TCT CCC CCT GTG C GCC TGC CTC TTG CTC TTCTGC GTC 234

5'-GGCCCGGGC-3' (FRAG. NO:1829) (SEQ. ID NO: 1842)

- 10 5'-GCCGGCGGGGGG 3' (FRAG. NO:1830) (SEQ. ID NO:1843)
  - 5'-GCCTGGGCTGGCC-3' (FRAG. NO:1831) (SEQ. ID NO: 1844)
  - 5'-GGGGG TGGCCG-3' (FRAG. NO:1832) (SEQ. ID NO: 1845)
  - 5'-GG GGG TGG CCG 'TG TGG GCG G-3' (FRAG. NO:1833) (SEQ. ID NO: 1846)
  - 5'-CGG TTT CCT TTG (CGG TC-3' (FRAG. NO:1260)(SEQ. ID NO:1269)
- 15 5'-TTG GCC CGG GCT CCG GGT G-3' (FRAG. NO:1261)(SEQ. ID NO:1270)
  - 5'-CCC GCC CGC CCG GCC GCC GC-3' (FRAG. NO:1262)(SEQ. ID NO:1271)
  - 5'-CCC GCC GGG CTG TCC CCG CCC CGC CCC-3' (FRAG. NO:1263)(SEQ. ID NO:1272)
  - 5'-GGC CCG GGG CGC GGG GG-3' (FRAG. NO:1264)(SEQ. ID NO:1273)
  - 5'-CGG CCC TCC CGC CCC TCT GG-3' (FRAG. NO:1265)(SEQ. ID NO:1274)
- 20 5'-GCC GGC GCG GGC GTC GG-3' (FRAG. NO:1266)(SEQ. ID NO:1275)
  - 5'-CCG CTC GCG CCT GGG GTT CCC TCT CCT CCC CCT GTG C-3' (FRAG. NO:1267)(SEQ. ID NO:1276)
  - 5'-GCC TGC CTC TTG CTC TTC-3' (FRAG. NO:1268)(SEQ. ID NO:1277)
  - 5'-TGC GTC CGC TGC CTT CTC CC-3' (FRAG. NO:1269)(SEO. ID NO:1278)
  - 5'CTC TCC TCG GCC (iTT GCC TGT GC-3' (FRAG. NO:1270)(SEQ. ID NO:1279)
- 25 5'-TGT CCG TCC TGT CGC CCT TCC GTG GTG C-3' (FRAG. NO:1271)(SEQ. ID NO:1280)
  - 5'-TGT TGT CTC T'GC CCT C-3' (FRAG. NO:1272)(SEQ. ID NO:1281)
    - 5'-GGT GTG CTG GTG GTG GTG GTG-3' (FRAG. NO:1273)(SEQ. ID NO:1282)
    - 5'-CCT CTG CCC GTG CTC GCC-3' (FRAG. NO:1274)(SEQ. ID NO:1283)
- 5'-CTG CCT GGG CTG GCC TCT TCG GGT-3' (FRAG. NO:1275)(SEQ. ID NO:1284)
- 5'-GTG GCT TTG GGG CTC TCT TGG TTG CCC TTT-3' (FRAG. NO:1276)(SEQ. ID NO:1285)
  - 5'-CTT CTC GTG GTG CCT CTC CTC CCT GGC TTG GTC GT-3' (FRAG. NO:1277)(SEQ. ID NO:1286)
  - 5'- TGT CTG GGG TGG TGC TCC TCT CCC-3' (FRAG. NO:1278)(SEQ. ID NO:1287)
  - 5'-TTT CCC TGC TGG CCG TTT GT-3' (FRAG. NO:1279)(SEQ. ID NO:1288)
  - 5'-CCT GTT TTC TGT CTT CCT CT-3' (FRAG. NO:1280)(SEQ. ID NO:1289)
- 5'-TTC CTC CTG TTT ('TC CGT-3' (FRAG. NO:1281)(SEQ. ID NO:1290)
  - 5'-TTG GCT TGC TGC 'ITG CGG GGC TGT CTC C-3' (FRAG. NO:1282)(SEQ. ID NO:1291)
  - 5'-CTT GCC CCT GTG GGC TTT CCC-3' (FRAG. NO:1283)(SEQ. ID NO:1292)
  - 5'-TGG TCC GGT CTT CTC CTT GGG GGT C-3' (FRAG. NO:1284)(SEO. ID NO:1293)
  - 5'-GCC CTT CTT GGT 13GG CTG-3' (FRAG. NO:1285)(SEQ. ID NO:1294)
- 40 5'-GCT CGT CTG TCT TTT TCC TTC C-3' (FRAG. NO:1286)(SEQ. ID NO:1295)
  - 5'-TGG GGG TGG CCG TTG TGG GCG GTG TGG TCC GCC T-3' (FRAG. NO:1287)(SEO. ID NO:1296)
  - 5'-TGC CTC TGC TGG TCT TTC-3' (FRAG. NO:1288)(SEQ. ID NO:1297)

## Human Interleukin 1 (IL-1) Nucleic Acid and antisense Oligocnucleotide Fragments

					-		
	5'-AAGCTTCTA	C CC AGTCTG	G TGCTACACT	Γ ACATTGCTTA	CATCCAAGTG	TGGTTATTTC	TGTGGCTCCT
45	GTTATAACTA	TTAT AGCACC	AGGTCTATGA	CCAGGAGAAT	TAGACTGGCA	TTAAATCAGA	ATAAGAGATT
	TTGCACCTGC	AATAGACCTT	ATGACACCTA	ACCAACCCCA	TTATTTACAA	TTAAACAGGA	ACAGAGGGAA
	TACTTTATCC	AACTCACACA	AGCTGTTTTC	CTCCCAGATC	CATGCTTTTT	TGCGTTTATT	ATTTTTTAGA
	GATGGGGGCT	TCA('TATGTT	GCCCACACTG	GACTAAAACT	CTGGGCCTCA	AGTGATTGTC	CTGCCTCAGC
	CTCCTGAATA	GCTGGGACTA	CAGGGGCATG	CCATCACACC	TAGTTCATTT	CCTCTATTTA	AAATATACAT
50	GGCTTAAACT	CCAA CTGGGA	ACCCAAAACA	TTCATTTGCT	AAGAGTCTGG	TGTTCTACCA	CCTGAACTAG
	GCTGGCCACA	GGAA.TTATAA	AAGCTGAGAA	ATTCTTTAAT	AATAGTAACC	AGGCAACATC	ATTGAAGGCT
	CATATGTAAA	AATCCATGCC	TTCCTTTCTC	CCAATCTCCA	TTCCCAAACT	TAGCCACTGG	TTCTGGCTGA
	GGCCTTACGC	ATAC CTCCCG	GGGCTTGCAC	ACACCTTCTT	CTACAGAAGA	CACACCTTGG	GCATATCCTA
	CAGAAGACCA	GGCTTCTCTC	TGGTCCTTGG	TAGAGGGCTA	CTTTACTGTA	ACAGGGCCAG	GGTGGAGAGT
55	TCTCTCCTGA	AGCT CCATCC	CCTCTATAGG	AAATGTGTTG	ACAATATTCA	GAAGAGTAAG	AGGATCAAGA
	CTTCTTTGTG	CTCA 4ATACC	ACTGTTCTCT	TCTCTACCCT	GCCCTAACCA	GGAGCTTGTC	ACCCCAAACT
	CTGAGGTGAT	TTATGCCTTA	ATCAAGCAAA	CTTCCCTCTT	CAGAAAAGAT	GGCTCATTTT	CCCTCAAAAG
	TTGCCAGGAG	CTGCCAAGTA	TTCTGCCAAT	TCACCCTGGA	GCACAATCAA	CAAATTCAGC	CAGAACACAA
	CTACAGCTAC	TATTAGAACT	ATTATTATTA	ATAAATTCCT	CTCCAAATCT	AGCCCCTTGA	CTTCGGATTT
60	CACGATTTCT	CCCTTCCTCC	TAGAAACTTG	ATAAGTTTCC	CGCGCTTCCC	TTTTTCTAAG	ACTACATGTT
	TGTCATCTTA	TAAAGCAAAG	GGGTGAATAA	ATGAACCAAA	TCAATAACTT	CTGGAATATC	TGCAAACAAC



	AATAATATCA	GCTA TGCCAT	CTTTCACTAT			ATGAACATAG	
	AACTGAATTC	TTCCCTGTAA	ATTCCCCGTT	TTGACGACGC	ACTTGTAGCC	ACGTAGCCAC	GCCTACTTAA
	GACAATTACA	AAAGGCGAAG	AAGACTGACT	CAGGCTTAAG	CTGCCAGCCA	GAGAGGGAGT	CATTTCATTG
	GCGTTTGAGT	CAGCAAAGGT	ATTGTCCTCA	CATCTCTGGC	TATTAAAGTA	TTTTCTGTTG	TTGTTTTTCT
5	CTTTGGCTGT	TTTCTCTCAC	ATTGCCTTCT	CTAAAGCTAC	AGTCTCTCCT	TTCTTTTCTT	GTCCCTCCCT
	GGTTTGGTAT	GTGA CCTAGA	ATTACAGTCA	GATTTCAGAA	AATGATTCTC	TCATTTTGCT	GATAAGGACT
	GATTCGTTTT	ACTG AGGGAC	GGCAGAACTA	GTTTCCTATG	AGGGCATGGG	TGAATACAAC	TGAGGCTTCT
	CATGGGAGGG	AATCTCTACT	ATCCAAAATT	ATTAGGAGAA	AATTGAAAAT	TTCCAACTCT	GTCTCTCTCT
	TACCTCTGTG	TAAC GCAAAT	ACCTTATTCT	TGTGGTGTTT	TTGTAACCTC	TTCAAACTTT	CATTGATTGA
10	ATGCCTGTTC	TGGCAATACA	TTAGGTTGGG	CACATAAGGA	ATACCAACAT	AAATAAAACA	TTCTAAAAGA
	AGTTTACGAT	CTAATAAAGG	AGACAGGTAC	ATAGCAAACT	AATTCAAAGG	AGCTAGAAGA	TGGAGAAAAT
	GCTGAATGTG	GACTAAGTCA	TTCAACAAAG	TTTTCAGGAA	GCACAAAGAG	GAGGGGCTCC	CCTCACAGAT
	ATCTGGATTA	GAGC CTGGCT	GAGCTGATGG	TGGCTGGTGT	TCTCTGTTGC	AGAAGTCAAG	ATGGCCAAAG
	TTCCAGACAT	GTTTGAAGAC	CTGAAGAACT	GTTACAGGTA	AGGAATAAGA	TTTATCTCTT	GTGATTTAAT
15	GAGGGTTTCA	AGGC TCACCA	GAATCCAGCT	AGGCATAACA	GTGGCCAGCA	TGGGGGCAGG	CCGGCAGAGG
	TTGTAGAGAT	GTGTACTAGT	CCTGAAGTCA	GAGCAGGTTC	AGAGAAGACC	CAGAAAAACT	AAGCATTCAG
	CATGTTAAAC	TGAC ATTACA	TTGGCAGGGA	GACCGCCATT	TTAGAAAAAT	TATTTTTGAG	GTCTGCTGAG
	CCCTACATGA	ATATCAGCAT	CAACTTAGAC	ACAGCCTCTG	TTGAGATCAC	ATGCCCTGAT	ATAAGAATGG
	GTTTTACTGG	TCCATTCTCA	GGAAAACTTG	ATCTCATTCA	GGAACAGGAA	ATGGCTCCAC	AGCAAGCTGG
20	GCATGTGAAC	TCACATATGC	AGGCAAATCT	CACTCAGATG	TAGAAGAAAG	GTAAATGAAC	ACAAAGATAA
	AATTACGGAA	CATATTAAAC	TAACATGATG	TTTCCATTAT	CTGTAGTAAA	TACTAACACA	AACTAGGCTG
	TCAAAATTTT	GCCTGGATAT	TTTACTAAGT	ATAAATTATG	AAATCTGTTT	TAGTGAATAC	ATGAAAGTAA
	TGTGTAACAT	ATA#TCTATT	TGGTTAAAAT	AAAAAGGAAG	TGCTTCAAAA	CCTTTCTTTT	CTCTAAAGGA
	GCTTAACATT	CTTCCCTGAA	CTTCAATTAA	AGCTCTTCAA	TTTGTTAGCC	AAGTCCAATT	TTTACAGATA
25	AAGCACAGGT	AAAGCTCAAA	GCCTGTCTTG	ATGACTACTA	ATTCCAGATT	AGTAAGATAT	GAATTACTCT
	ACCTATGTGT	ATGTGTAGAA	GTCCTTAAAT	TTCAAAGATG	ACAGTAATGG	CCATGTGTAT	GTGTGTGACC
	CACAACTATC	ATGC TCATTA	AAGTACATTG	GCCAGAGACC	ACATGAAATA	ACAACAATTA	CATTCTCATC
	ATCTTATTTT	GACAGTGAAA	ATGAAGAAGA	CAGTTCCTCC	ATTGATCATC	TGTCTCTGAA	TCAGGTAAGC
	AAATGACTGT	AATT'CTCATG	GGACTGCTAT	TCTTACACAG	TGGTTTCTTC	ATCCAAAGAG	AACAGCAATG
30	ACTTGAATCT	TAAA TACTTT	TGTTTTACCC	TCACTAGAGA	TCCAGAGACC	TGTCTTTCAT	TATAAGTGAG
	ACCAGCTGCC	TCTCTAAACT	AATAGTTGAT	GTGCATTGGC	TTCTCCCAGA	ACAGAGCAGA	ACTATCCCAA
	ATCCCTGAGA	ACTC GAGTCT	CCTGGGGCAG	GCTTCATCAG	GATGTTAGTT	ATGCCATCCT	GAGAAAGCCC
	CGCAGGCCGC	TTCACCAGGT	GTCTGTCTCC	TAACGTGATG	TGTTGTGGTT	GTCTTCTCTG	ACACCAGCAT
	CAGAGGTTAG	AGA#.AGTCTC	CAAACATGAA	GCTGAGAGAG	AGGAAGCAAG	CCAGCTGAAA	GTGAGAAGTC
35	TACAGCCACT	CATC AATCTG	TGTTATTGTG	TTTGGAGACC	ACAAATAGAC	ACTATAAGTA	CTGCCTAGTA
	TGTCTTCAGT	ACTGGCTTTA	AAAGCTGTCC	CCAAAGGAGT	ATTTCTAAAA	TATTTTGAGC	ATTGTTAAGC
	AGATTTTTAA	CCTCCTGAGA	GGGAACTAAT	TGGAAAGCTA	CCACTCACTA	CAATCATTGT	TAACCTATTT
	AGTTACAACA	TCT('ATTTTT	GAGCATGCAA	ATAAATGAAA	AAGTCTTCCT	AAAAAAATCA	TCTTTTTATC
	CTGGAAGGAG	GAAGGAAGGT		GGAGAGAGGG	AGGGAAGCCT	AATGAAACAC	CAGTTACCTA
40	AGACCAGAAT	GGAGATCCTC	CTCACTACCT	CTGTTGAATA	CAGCACCTAC	TGAAAGAACT	TTCATTCCCT
	GACCATGAAC	AGCCTCTCAG	CTTCTGTTTT	CCTTCCTCAC	AGAAATCCTT	CTATCATGTA	AGCTATGGCC
	CACTCCATGA	AGGCTGCATG	GATCAATCTG	TGTCTCTGAG	TATCTCTGAA	ACCTCTAAAA	CATCCAAGCT
						AGAAGAGACG	
						GGAAGGTAAG	
45						AGGGGAAAAT	
						GAAAATTAAT	
						AGCCATTATT	
						ACCACTTACG	
<b>.</b>						TTCAGTTTCC	
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						CCCTAACTTC	
						TTATTATTAT	
						GCACAATCTC	
						AAGCTGGGAA	
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						CACCGCGCCC	
						ATTTATTAAT	
						TAAGCTCATT	
<b>C</b> C						AGTTCTACCT	
60						TAAACCCAAT	
						TGTAACAAAA	
	TAAAAATCAC	TCATATCGTC	AGTGAGAGTT	TACTACTGCC	AGCACTATGG	TATGTTTCCT	TAAAATCTTT



	GCTATACACA	TACCTACATG	TGAACAAATA	TGTCTAACAT	CAAGACCACA	CTATTTACAA	CTTTATATCC
	AGCTTTTCTT	ACTT AGCAAT	GTATTGAGGA	CATTTTAGAG	TGCCCGTTTT	TCACCATTAT	AAGCAATGCA
	ACAATGAACA	TCTGTATAAA	TAAATATTCA	TTTCTCTCAC	CCTTTATTTC	CTTAGAATAT	ATTCCTAGAA
	GTAGAATTTC	CCAGAGCCAT	GAGGATTTGT	GACGCTATTG	ATATGTGCCA	CTTTGCACTC	TCTGTGACAT
5	ATATAATTAT	TTTTAATGCA	TTCATTTTTT	TCTCAGAGTG	CATTCGTTTG	AAAACATAGA	CGGGAAATAC
	TGGTAGTCTT	CCTT 3TCAGT	TAGAAACACC	CAAACAATGA	AAAATGAAAA	AGTTGCACAA	ATAGTCTCTA
	AAAACAATGA	AACT ATTGCC	TGAGGAATTG	AAGTTTAAAA	AGAAGCACAT	AAGCAACAAC	AAGGATAATC
	CTAGAAAACC	AGT CTGCTG	ACTGGGTGAT	TTCACTTCTC	TTTGCTTCCT	CATCTGGATT	GGAATATTCC
	TAATACCCCC	TCCA.GAACTA	TTTTCCCTGT	TTGTACTAGA	CTGTGTATAT	CATCTGTGTT	TGTACATAGA
10	CATTAATCTG	CACITGTGAT	CATGGTTTTA	GAAATCATCA	AGCCTAGGTC	ATCACCTTTT	AGCTTCCTGA
	GCAATGTGAA	ATACAACTTT	ATGAGGATCA	TCAAATACGA	ATTCATCCTG	AATGACGCCC	TCAATCAAAG
	TATAATTCGA	GCCA ATGATC	AGTACCTCAC	GGCTGCTGCA	TTACATAATC	TGGATGAAGC	AGGTACATTA
	AAATGGCACC	AGACATTTCT	GTCATCCTCC	CCTCCTTTCA	TTTACTTATT	TATTTATTTC	AATCTTTCTG
	CTTGCAAAAA	ACATACCTCT	TCAGAGTTCT	GGGTTGCACA	ATTCTTCCAG	AATAGCTTGA	AGCACAGCAC
15	CCCCATAAAA	ATCC CAAGCC	AGGGCAGAAG	GTTCAACTAA		TCCACAAGAG	AGAAGTTTCC
13	TATCTTTGAG	AGT# AAGGGT	TGTGCACAAA	GCTAGCTGAT	GTACTACCTC	TTTGGTTCTT	TCAGACATTC
	TTACCCTCAA	TTTTAAAACT	GAGGAAACTG	TCAGACATAT	TAAATGATTT		
	CAATGAAGAA	CAA^CACTCT				ACTCAGATTT	ACCCAGAAGC
	ATCTTTATTA	TCTCTGATAA	CATATTTCTC	GTCTGTTGAT		AGTAACACCA	AACCAGGAAG
20			CATATTTGTG	AGGCAAAACC	TCCAATAAGC	TACAAATATG	GCTTAAAGGA
20	TGAAGTTTAG	TGTC'CAAAAA	CTTTTATCAC	ACACATCCAA	TTTTCATGGC	GGACATGTTT	TAGTTTCAAC
	AGTATACATA	TTTTCAAAGG	TCCAGAGAGG	CAATTTTGCA	ATAAACAAGC	AAGACTTTTT	CTGATTGGAT
	GCACTTCAGC	TAACATGCTT	TCAACTCTAC	ATTTACAAAT	TATTTTGTGT	TCTATTTTC	TACTTAATAT
	TATTTCTGCA	ATTTTCCCAA	TATTGACATC	GTGTATGTAT	TTGCCATTTT	TAATATCACT	AGACAATTCA
25	ATCAGGTTGC	TACGTTGGTC	CCTTGGGTTT	ACTCTAAATA	GCTTGATTGC	AAATATCTTT	GTATATATTA
25					CAAAGAGGAA	TGCCTAGATC	AATGGGCACA
	AATAATTTGA	CAGCTCTTAT	TAAACATTAT	TCTGTAAGTA	AAAACTGAAC	TACTTTTCAG	TATCACTAGC
	AACATATGAG	TGTATCAGCT	TCCTAAACCC	CTCCATGTTA	GGTCATTATG	AACTTATGAT	CTAACAAATT
	ACAGGGTCTT	ATCC CACTAA	TGAAATTATA	AGAGATTCAA	CACTTATTCA	GCCCCGAAGG	ATTCATTCAA
••	CGTAGAAAAT	TCT#AGAACA	TTAACCAAGT	ATTTACCTGC	CTAGTGAGTG	TGGAAGACAT	TGTGAAGGAC
30	ACAAAGATGT	ATAGAATTCC	ATTCCTGACT	TCCAGGTATT	TACACCATAG	GTGGGGACCT	AACTACACAC
	ACACACACAC	ACACACACAC	ACACACACAC		CACAATCTAC	ATCAACACTT	GATTTTATAC
	AAATACAATG	AATTTACTTT	CTTTTTGGTT	CTTCTCTTCA	CCAGTGAAAT	TTGACATGGG	TGCTTATAAG
	TCATCAAAGG	ATGATGCTAA	AATTACCGTG	ATTCTAAGAA	TCTCAAAAAC	TCAATTGTAT	GTGACTGCCC
	AAGATGAAGA	CCAACCAGTG	CTGCTGAAGG	TCAGTTGTCC		ACTTACCTTC	ATTTACATCT
35	CATATGTTTG	TAAATAAGCC	CAATAGGCAG	ACACCTCTAA	CAAGGTGACA	CTGTCCTCTT	TCCTTCCTAC
	CACAGCCCCC	ACCTACCCAC	CCCACTCCCA		AGGCGTGCCT	AGGCAGGATC	TATGAGAAAA
	TATAACAGAG	AGT.\AGAGGA	AAATTACCTT	CTTTCTTTTT	CCTTTCCCTG	CCTGACCTTA	TTCACCTCCC
	ATCCCAGAGC	ATCCATTTAT	TCCATTGATC	TTTACTGACA	TCTATTATCT	GACCTACACA	ATACTAGACA
	TTAGGACAAT	GTGC CCTGCC	TCCAAGAAAC	TCAAATAAGC	CAACTGAGAT	CAGAGAGGAT	TAATCACCTG
40	CCAATGGGCA	CAAAGCAACA	AGCTGGGAGC	CAAGTCCCAA	AATGGGGCCT	GCTGCTTCCA	GTTCCCCTCT
	CTCTGCATTG	ATG1 CAGCAT	TATCCTTCGT	CCCAGTCCTG	TCTCCACTAC	CACTTTCCCC	CTCAAACACA
	CACACACACA	ACAGCCTTAG	ATGTTTTCTC	CACTGATAAG	TAGGTGACTC	AATTTGTAAG	TATATAATCC
					TGCTTTTCTA		
	CAGAGTAGGG	CAG'l'AGCTTC	ATTCATGAAC	TCATTCAACA	AGCATTATTC	ACTGAGAGCC	TTGTATTTT
45	CAGGCATAGT	GCCAACAGCA	GTGTGGACAG	TGGTGCATCA	AAGCCTCTAG	TCTCATAGAA	CTTAGTCTTC
	TGGAGGATAT	GGAA.AACAGA	CAACCCAAAC	AACCAACAAA	AGAGCAAGAT	GCTGCAAAAA	AAAAAAAAT
	GAATAGGGTG	CTA/.GATAGA	GAAAAGTGGG	AGAGTGCTAT	TTAGACAAAG	TGGTAAAAAC	AAAGCCCCTT
	GTGAGATGAG	AGCT'GCCGAC	AGAGGGGGCG	GGTCATGGTT	GTGGGTTTTT	GGGTAGGACA	TTCAGAGGAG
	GGGGCGGGTC	GTGGTTGTGG	GTTTTTGGGT	AGGACATTCA	GAGGAGGGG	CGGGTCGTGG	TTGTGGGTTT
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	GGCGGGTCGT	GGT1'GTGGGT	TTTTGGGACA	TTCAGAGGAG	TCTGAATGCA	CCCAGGCCTA	CAACTTCAAG
					GGAACTGGGG		
	ATATGCAGAG	ACTAGTGCTT	GCAGAGCTTG	CATTTGGATT	TCATTTGAGG	TACAATGAAA	ACCCATTAAT
					CCTAAAATAG		
55					AGTCATGGGG		
					AACCAACAGA		
					AAATAAATCC		
					AGAATAGGAA		
					CTCATACTCA		
60					GTGTGTATGT		
-					AATGTCATCT		
					GGGCTTAGAA		
				3111100	JUJUTA	Londing	JULUIGHIII



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	GATGCAAAAT	GTCTTAGGCC		GCAGGACAGA			TGCCTGGATA
	CAGTAAGATA	CTAGTGTCAC	TGACAATCTT	CATAACTAAT	TTAGATCTCT	CTCCAATCAA	CTAAGGAAAT
	CAACTCTTAT	TAATAGACTG	GGCCACACAT	CTACTAGGCA	TGTAATAAAT	GCTTGCTGAA	TGAACAAATG
_	AATGAAGAGC	CTA 'AGCATC	ATGTTACAGC		AAGTGGTGTT	TCTCATGAAG	GCCAAATGCT
5	AAGGGATTGA	GCTTCAGTCC	TTTTTCTAAC	ATCTTGTTCT	CTAACAGAAT	TCTCTTCTTT	TCTTCATAGG
	AGATGCCTGA	GATACCCAAA	ACCATCACAG			TTCTTCTGGG	AAACTCACGG
	CACTAAGAAC	TATTTCACAT	CAGTTGCCCA	TCCAAACTTG	TTTATTGCCA	CAAAGCAAGA	CTACTGGGTG
	TGCTTGGCAG	GGGGGCCACC	CTCTATCACT	GACTTTCAGA	TACTGGAAAA	CCAGGCGTAG	GTCTGGAGTC
	TCACTTGTCT	CACTIGTGCA	GTGTTGACAG	TTCATATGTA	CCATGTACAT	GAAGAAGCTA	AATCCTTTAC
10	TGTTAGTCAT	TTGCTGAGCA	TGTACTGAGC	CTTGTAATTC	TAAATGAATG	TTTACACTCT	TTGTAAGAGT
	GGAACCAACA	CTAACATATA		TTAAAGAACA		TGCATAGTAC	CAATCATTTT
	AATTATTATT	CTTC ATAACA	ATTTTAGGAG	GACCAGAGCT	ACTGACTATG	GCTACCAAAA	AGACTCTACC
	CATATTACAG	ATGGGCAAAT	TAAGGCATAA	GAAAACTAAG	AAATATGCAC		GAAACAAGAA
	GCCACAGACC	TAGGATTTCA	TGATTTCATT	TCAACTGTTT	GCCTTCTGCT	TTTAAGTTGC	TGATGAACTC
15	TTAATCAAAT	AGCATAAGTT	TCTGGGACCT	CAGTTTTATC	ATTTTCAAAA	TGGAGGGAAT	AATACCTAAG
	CCTTCCTGCC	GCAA CAGTTT	TTTATGCTAA	TCAGGGAGGT	CATTTTGGTA	AAATACTTCT	CGAAGCCGAG
	CCTCAAGATG	AAGGCAAAGC				ATATGTATTT	ATAAATATAT
	TTAAGATAAT	TATA ATATAC	TATATTTATG	GGAACCCCTT	CATCCTCTGA	GTGTGACCAG	GCATCCTCCA
• •	CAATAGCAGA	CAGTGTTTTC	TGGGATAAGT	AAGTTTGATT	TCATTAATAC	AGGGCATTTT	GGTCCAAGTT
20	GTGCTTATCC	CATAGCCAGG	AAACTCTGCA	TTCTAGTACT	TGGGAGACCT	GTAATCATAT	AATAAATGTA
	CATTAATTAC	CTTGAGCCAG	TAATTGGTCC	GATCTTTGAC	TCTTTTGCCA	TTAAACTTAC	CTGGGCATTC
	TTGTTTCATT	CAATICCACC	TGCAATCAAG	TCCTACAAGC	TAAAATTAGA	TGAACTCAAC	TTTGACAACC
	ATGAGACCAC	TGTT'ATCAAA	ACTTTCTTTT	CTGGAATGTA	ATCAATGTTT	CTTCTAGGTT	CTAAAAATTG
	TGATCAGACC	ATAATGTTAC	ATTATTATCA	ACAATAGTGA	TTGATAGAGT	GTTATCAGTC	ATAACTAAAT
25	AAAGCTTGCA	ACAAAATTCT	CTGACACATA		GCCTTAATCA	TTATTTTACT	GCATGGTAAT
	TAGGGACAAA	TGGTAAATGT			AGTGTTACTT	TATAAAATCA	AACCAAGATT
	TTATATTTTT	TTCTCCTCTT	TGTTAGCTGC	CAGTATGCAT	AAATGGCATT	AAGAATGATA	ATATTTCCGG
	GTTCACTTAA	AGCTCATATT	ACACATACAC	AAAACATGTG	TTCCCATCTT	TATACAAACT	CACACATACA
20				GCACGGTGGC			
30	ACCAACCTCT	TCGAGGCACA	AGGCACAACA			CAGCCAATCT	TCATTGCTCA
	AGTGTCTGAA	GCAGCCATGG	CAGAAGTACC		AGTGAAATGA		CAGTGGCAAT
	GAGGATGACT	TGTTCTTTGA	AGCTGATGGC	CCTAAACAGA	TGAAGTGCTC	CTTCCAGGAC	CTGGACCTCT
	GCCCTCTGGA	TGGC GGCATC	CAGCTACGAA	TCTCCGACCA	CCACTACAGC	AAGGGCTTCA	GGCAGGCCGC
25	GTCAGTTGTT	GTGGCCATGG	ACAAGCTGAG	GAAGATGCTG	GTTCCCTGCC	CACAGACCTT	CCAGGAGAAT
35	GACCTGAGCA	CCTTCTTTCC	CTTCATCTTT	GAAGAAGAAC	CTATCTTCTT	CGACACATGG	GATAACGAGG
	CTTATGTGCA	CGATGCACCT	GTACGATCAC	TGAACTGCAC	GCTCCGGGAC	TCACAGCAAA	AAAGCTTGGT
	GATGTCTGGT	CCATATGAAC	TGAAAGCTCT	CCACCTCCAG	GGACAGGATA	TGGAGCAACA	AGTGGTGTTC
	TCCATGTCCT	TTGT.ACAAGG	AGAAGAAAGT	AATGACAAAA	TACCTGTGGC	CTTGGGCCTC	AAGGAAAAGA
40	ATCTGTACCT	GTCCTGCGTG	TTGAAAGATG AAAAGCGATT	ATAAGCCCAC	TCTACAGCTG	GAGAGTGTAG	ATCCCAAAAA
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	GAGTCTGCCC GGACCAAAGG	AGTTCCCCAA CGGCCAGGAT	CTGGTACATC	AGCACCTCTC TCACCATGCA	AAGCAGAAAA	CATGCCCGTC TCCTAAAGAG	TTCCTGGGAG AGCTGTACCC
				CCCTAGGGCT ACACCAATGC			
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				CTGATGAGCA			
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				TGGACTGGTG			
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				CAGTGTTAGG			
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00				AAATTAAAAA			
				TTCCCTCGTG			
				GCACATACTA			
				CTGAATGTAC			
60				GGGCAAGGTT			
				AACATTTGGG			
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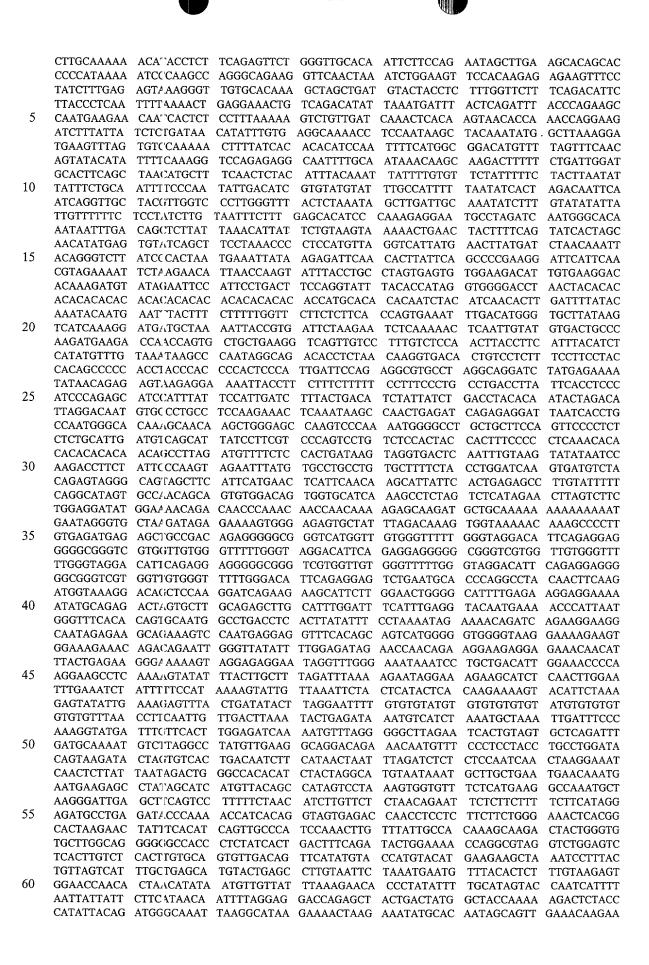


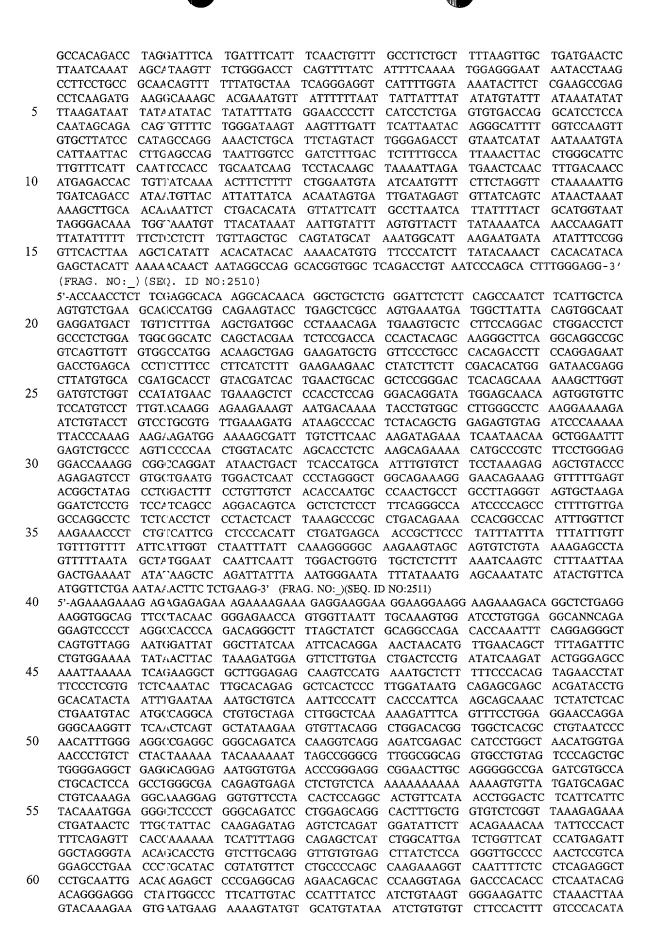
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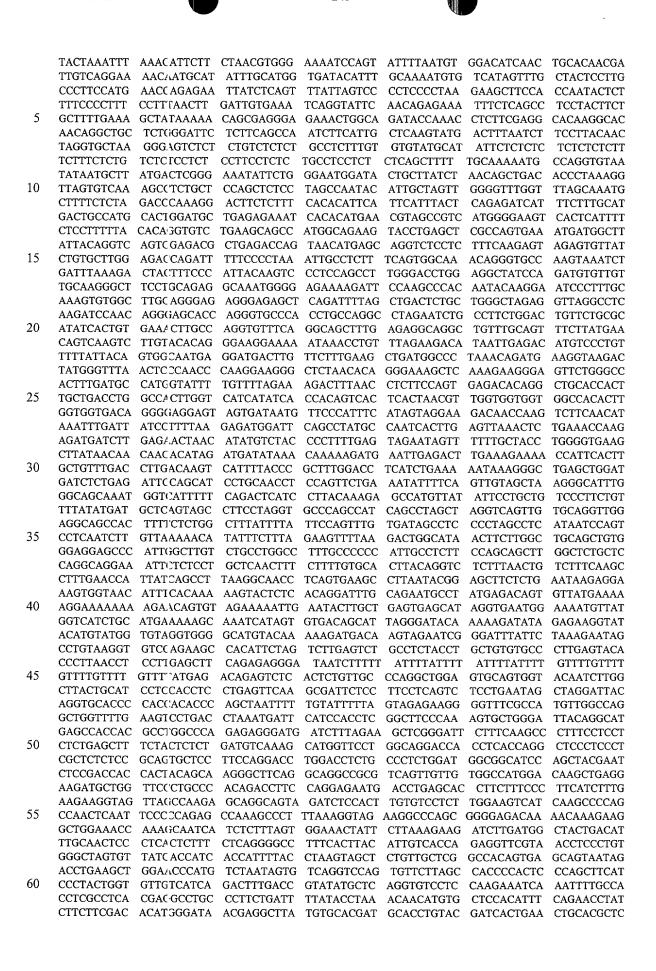


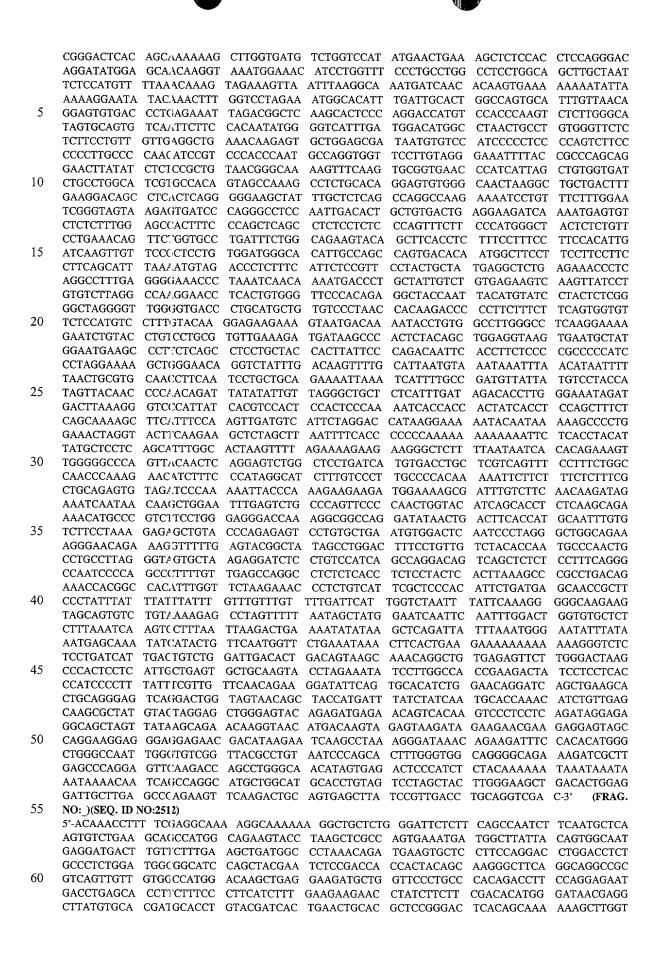


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35	GTCAGAATAA CTCCAGGAGG	CAAGAAGACA GAGAAATGAG TCG1'GTGACT AAC1'ATGCCT	ACCAAGCATT CAGTGGCCTG TTTAGCCTTT CCTTGGTCAT	AAGTAGGGAC AGTCTGGTAA AATCGAGAAT	AGTAGAATTT CTATACAGAG ACTTGCTCAC	AGGGGAAAAT GAAAATTAAT AGCCATTATT	TAAACGTGGA TTTTATCCTT TCTTAGCCAT AGCTATGTTC TCTACTGTAA
35	GTCAGAATAA CTCCAGGAGG ATTGTAAAGG	CAAGAAGACA GAGAAATGAG TCGTGTGACT	ACCAAGCATT CAGTGGCCTG TTTAGCCTTT	AAGTAGGGAC AGTCTGGTAA AATCGAGAAT CAGGAGAAAG	AGTAGAATTT CTATACAGAG ACTTGCTCAC CAGTAATAAG	AGGGGAAAAT GAAAATTAAT AGCCATTATT ACCACTTACG	TAAACGTGGA TTTTATCCTT TCTTAGCCAT AGCTATGTTC
35	GTCAGAATAA CTCCAGGAGG ATTGTAAAGG CTCTCATACT	CAAGAAGACA GAGAAATGAG TCGTGTGACT AACTATGCCT ATCAGAATCC GGCCCTCCTG	ACCAAGCATT CAGTGGCCTG TTTAGCCTTT CCTTGGTCAT	AAGTAGGGAC AGTCTGGTAA AATCGAGAAT CAGGAGAAAG GTTACATAAT	AGTAGAATTT CTATACAGAG ACTTGCTCAC CAGTAATAAG CTTTTCGTGA	AGGGGAAAAT GAAAATTAAT AGCCATTATT ACCACTTACG TTCAGTTTCC AGTCTCAGGC CCCTAACTTC	TAAACGTGGA TTTTATCCTT TCTTAGCCAT AGCTATGTTC TCTACTGTAA
	GTCAGAATAA CTCCAGGAGG ATTGTAAAGG CTCTCATACT AATGGAGATA	CAAGAAGACA GAGAAATGAG TCG1'GTGACT AAC1'ATGCCT ATCAGAATCC GGCCCTCCTG TACAAAGTAA	ACCAAGCATT CAGTGGCCTG TTTAGCCTTT CCTTGGTCAT CCCACTCATT ACTGTTATAA GCACCCAATA	AAGTAGGGAC AGTCTGGTAA AATCGAGAAAG CAGGAGAAAAG GTTACATAAT GGATTGTTGT AGATTAAATG AATGTTAGCT	AGTAGAATTT CTATACAGAG ACTTGCTCAC CAGTAATAAG CTTTTCGTGA AAAGATTAAG AGTCAACATC	AGGGGAAAAT GAAAATTAAT AGCCATTATT ACCACTTACG TTCAGTTTCC AGTCTCAGGC CCCTAACTTC TTATTATTAT	TAAACGTGGA TTTTATCCTT TCTTAGCCAT AGCTATGTTC TCTACTGTAA TTTACAGACT TGGACTAGAA TATTTTATTT
35 40	GTCAGAATAA CTCCAGGAGG ATTGTAAAGG CTCTCATACT AATGGAGATA GAGCTAGCTG TAATGTCTGG TTTTTTTTTT	CAAGAAGACA GAGAAATGAG TCGTGTGACT AACTATGCCT ATCAGAATCC GGCCCTCCTG TACAAAGTAA AGATGGAGTC	ACCAAGCATT CAGTGGCCTG TTTAGCCTTT CCTTGGTCAT CCCACTCATT ACTGTTATAA GCACCCAATA TGGCTCTGTC	AAGTAGGGAC AGTCTGGTAA AATCGAGAAAG CAGGAGAAAG GTTACATAAT GGATTGTTGT AGATTAAATG AATGTTAGCT ACCCAGGCTG	AGTAGAATTT CTATACAGAG ACTTGCTCAC CAGTAATAAG CTTTTCGTGA AAAGATTAAG AGTCAACATC ATTACTATCA GAGTGCAGTG	AGGGGAAAAT GAAAATTAAT AGCCATTATT ACCACTTACG TTCAGTTTCC AGTCTCAGGC CCCTAACTTC TTATTATTAT GCACAATCTC	TAAACGTGGA TTTTATCCTT TCTTAGCCAT AGCTATGTTC TCTACTGTAA TTTACAGACT TGGACTAGAA TATTTTATTT
	GTCAGAATAA CTCCAGGAGG ATTGTAAAGG CTCTCATACT AATGGAGATA GAGCTAGCTG TAATGTCTGG TTTTTTTTTT	CAAGAAGACA GAGAAATGAG TCG1'GTGACT AAC1'ATGCCT ATCAGAATCC GGCCCTCCTG TACAAAGTAA	ACCAAGCATT CAGTGGCCTG TTTAGCCTTT CCTTGGTCAT CCCACTCATT ACTGTTATAA GCACCCAATA	AAGTAGGGAC AGTCTGGTAA AATCGAGAAAG CAGGAGAAAAG GTTACATAAT GGATTGTTGT AGATTAAATG AATGTTAGCT	AGTAGAATTT CTATACAGAG ACTTGCTCAC CAGTAATAAG CTTTTCGTGA AAAGATTAAG AGTCAACATC ATTACTATCA	AGGGGAAAAT GAAAATTAAT AGCCATTATT ACCACTTACG TTCAGTTTCC AGTCTCAGGC CCCTAACTTC TTATTATTAT	TAAACGTGGA TTTTATCCTT TCTTAGCCAT AGCTATGTTC TCTACTGTAA TTTACAGACT TGGACTAGAA TATTTTATTT
	GTCAGAATAA CTCCAGGAGG ATTGTAAAGG CTCTCATACT AATGGAGATA GAGCTAGCTG TAATGTCTGG TTTTTTTTTT	CAAGAAGACA GAGAAATGAG TCGTGTGACT AACTATGCCT ATCAGAATCC GGCCCTCCTG TACAAAGTAA AGATGGAGTC	ACCAAGCATT CAGTGGCCTG TTTAGCCTTT CCTTGGTCAT CCCACTCATT ACTGTTATAA GCACCCAATA TGGCTCTGTC	AAGTAGGGAC AGTCTGGTAA AATCGAGAAAG CAGGAGAAAG GTTACATAAT GGATTGTTGT AGATTAAATG AATGTTAGCT ACCCAGGCTG	AGTAGAATTT CTATACAGAG ACTTGCTCAC CAGTAATAAG CTTTTCGTGA AAAGATTAAG AGTCAACATC ATTACTATCA GAGTGCAGTG	AGGGGAAAAT GAAAATTAAT AGCCATTATT ACCACTTACG TTCAGTTTCC AGTCTCAGGC CCCTAACTTC TTATTATTAT GCACAATCTC	TAAACGTGGA TTTTATCCTT TCTTAGCCAT AGCTATGTTC TCTACTGTAA TTTACAGACT TGGACTAGAA TATTTTATTT
	GTCAGAATAA CTCCAGGAGG ATTGTAAAGG CTCTCATACT AATGGAGATA GAGCTAGCTG TAATGTCTGG TTTTTTTTTG AAGCTCTGCC CGCCACTGTT GTGATCCACC	CAAGAAGACA GAGAAATGAG TCGTGTGACT AACTATGCCT ATCAGAATCC GGCCCTCCTG TACAAAGTAA AGATGGAGTC TCCTGGGTTC CCCCGGCTAAT CACCTTGGCC	ACCAAGCATT CAGTGGCCTG TTTAGCCTTT CCTTGGTCAT CCCACTCATT ACTGTTATAA GCACCCAATA TGGCTCTGTC ATGCCATTCT TTTTTGTATT TCCCAAAGTG	AAGTAGGAC AGTCTGGTAA AATCGAGAAAG GTTACATAAT GGATTGTTGT AGATTAAATG AATGTTAGCT ACCCAGGCTG CCTGCCTCAG TTTAGTAGAG CCGGGATTAC	AGTAGAATTT CTATACAGAG ACTTGCTCAC CAGTAATAAG CTTTTCGTGA AAAGATTAAG AGTCAACATC ATTACTATCA GAGTGCAGTG CCTCCCGAGT ACGGAGTTTC AGGCGTGAGC	AGGGGAAAAT GAAAATTAAT AGCCATTACG TTCAGTTTCC AGTCTCAGGC CCCTAACTTC TTATTATTAT GCACAATCTC AAGCTGGGAA ACCGTGGTCT CACCGCCCC	TAAACGTGGA TTTTATCCTT TCTTAGCCAT AGCTATGTTC TCTACTGTAA TTTACAGACT TGGACTAGAA TATTTTATTT
40	GTCAGAATAA CTCCAGGAGG ATTGTAAAGG CTCTCATACT AATGGAGATA GAGCTAGCTG TAATGTCTGG TTTTTTTTTG AAGCTCTGCC CGCCACTGTT GTGATCCACC TATTATTATT	CAAGAAGACA GAGAAATGAG TCGTGTGACT AACTATGCCT ATCAGAATCC GGCCCTCCTG TACAAAGTAA AGATGGAGTC TCCTGGGTTC CCCGGCTAAT CACCTTGGCC ACTACTACTA	ACCAAGCATT CAGTGGCCTG TTTAGCCTTT CCTTGGTCAT CCCACTCATT ACTGTTATAA GCACCCAATA TGGCTCTGTC ATGCCATTCT TTTTTGTATT TCCCAAAGTG CTACCTATAT	AAGTAGGGAC AGTCTGGTAA AATCGAGAAAG GTTACATAAT GGATTGTTGT AGATTAAATG AATGTTAGCT ACCCAGGCTG CCTGCCTCAG TTTAGTAGAG CCGGGATTAC GAATACTACC	AGTAGAATTT CTATACAGAG ACTTGCTCAC CAGTAATAAG CTTTTCGTGA AAAGATTAAG AGTCAACATC ATTACTATCA GAGTGCAGTG CCTCCCGAGT ACGGAGTTTC AGGCGTGAGC AGCAATACTA	AGGGGAAAAT GAAAATTAAT AGCCATTACG TTCAGTTTCC AGTCTCAGGC CCCTAACTTC TTATTATTAT GCACAATCTC AAGCTGGGAA ACCGTGGTCT CACCGCGCCC ATTTATTAAT	TAAACGTGGA TTTTATCCTT TCTTAGCCAT AGCTATGTTC TCTACTGTAA TTTACAGACT TGGACTAGAA TATTTTATTT
	GTCAGAATAA CTCCAGGAGG ATTGTAAAGG CTCTCATACT AATGGAGATA GAGCTAGCTG TAATGTCTGG TTTTTTTTTG AAGCTCTGCC CGCCACTGTT GTGATCCACC TATTATTATT TGTCTAAACC	CAAGAAGACA GAGAAATGAG TCGTGTGACT AACTATGCCT ATCAGAATCC GGCCCTCCTG TACAAAGTAA AGATGGAGTC TCCTGGGTTC CCCGGCTAAT CACCTTGGCC ACTACTACTA TCACAAGAAT	ACCAAGCATT CAGTGGCCTG TTTAGCCTTT CCTTGGTCAT CCCACTCATT ACTGTTATAA GCACCCAATA TGGCTCTGTC ATGCCATTCT TTTTTGTATT TCCCAAAGTG CTACCTATAT CCTACCTTCT	AAGTAGGGAC AGTCTGGTAA AATCGAGAAAG GTTACATAAT GGATTGTTGT AGATTAAATG AATGTTAGCT ACCCAGGCTG CCTGCCTCAG TTTAGTAGAG CCGGGATTAC GAATACTACC CATTTTACAT	AGTAGAATTT CTATACAGAG ACTTGCTCAC CAGTAATAAG CTTTTCGTGA AAAGATTAAG AGTCAACATC ATTACTATCA GAGTGCAGTG CCTCCCGAGT ACGGAGTTTC AGGCGTGAGC AGCAATACTA AAAAGGAAAC	AGGGGAAAAT GAAAATTAAT AGCCATTACG TTCAGTTTCC AGTCTCAGGC CCCTAACTTC TTATTATTAT GCACAATCTC AAGCTGGGAA ACCGTGGTCT CACCGCGCCC ATTTATTAAT TAAGCTCATT	TAAACGTGGA TTTTATCCTT TCTTAGCCAT AGCTATGTTC TCTACTGTAA TTTACAGACT TGGACTAGAA TATTTTATTT
40	GTCAGAATAA CTCCAGGAGG ATTGTAAAGG CTCTCATACT AATGGAGATA GAGCTAGCTG TAATGTCTGG TTTTTTTTTT	CAAGAAGACA GAGAAATGAG TCGI'GTGACT AACI'ATGCCT ATCAGAATCC GGCCCTCCTG TACAAAGTAA AGATGAGTC TCCI GGGTTC CCCCIGCTAAT CACCTTTGGCC ACTACTACTA TCAC AAGAAT	ACCAAGCATT CAGTGGCCTG TTTAGCCTTT CCTTGGTCAT CCCACTCATT ACTGTTATAA GCACCCAATA TGGCTCTGTC ATGCCATTCT TTTTTGTATT TCCCAAAGTG CTACCTATAT CCTACCTTCT CTGTAAGTGG	AAGTAGGGAC AGTCTGGTAA AATCGAGAAAG GTTACATAAT GGATTGTTGT AGATTAAATG AATGTTAGCT ACCCAGGCTG CCTGCCTCAG TTTAGTAGAG CCGGGATTAC GAATACTACC CATTTTACAT GAGAGCCTCA	AGTAGAATTT CTATACAGAG ACTTGCTCAC CAGTAATAAG CTTTTCGTGA AAAGATTAAG AGTCAACATC ATTACTATCA GAGTGCAGTG CCTCCCGAGT ACGGAGTTTC AGGCGTGAGC AGCAATACTA AAAAGGAAAC AATCTAATTC	AGGGGAAAAT GAAAATTAAT AGCCATTACG TTCAGTTTCC AGTCTCAGGC CCCTAACTTC TTATTATTAT GCACAATCTC AAGCTGGGAA ACCGTGGTCT CACCGCGCCC ATTTATTATAT TAAGCTCATT AGTTCTACCT	TAAACGTGGA TTTTATCCTT TCTTAGCCAT AGCTATGTTC TCTACTGTAA TTTACAGACT TGGACTAGAA TATTTTATTT
40	GTCAGAATAA CTCCAGGAGG ATTGTAAAGG CTCTCATACT AATGGAGATA GAGCTAGCTG TAATGTCTGG TTTTTTTTTG AAGCTCTGCC CGCCACTGTT GTGATCCACC TATTATTATT TGTCTAAACC AACTGCCCAA ATCATGGTTT	CAAGAAGACA GAGAAATGAG TCGI'GTGACT AACI'ATGCCT ATCAGAATCC GGCCCTCCTG TACAAAGTAA AGATGGAGTC TCCIGGGTTC CCCGGCTAAT CACCTTGGCC ACTACTACTA TCACAAGAAT TGGCATACAT CTCCTCCATC	ACCAAGCATT CAGTGGCCTG TTTAGCCTTT CCTTGGTCAT CCCACTCATT ACTGTTATAA GCACCCAATA TGGCTCTGTC ATGCCATTCT TTTTTGTATT TCCCAAAGTG CTACCTATAT CCTACCTTCT CTGTAAGTGG CCTTTACTGT	AAGTAGGGAC AGTCTGGTAA AATCGAGAAAG GTTACATAAT GGATTGTTGT AGATTAAATG AATGTTAGCT ACCCAGGCTG CCTGCCTCAG TTTAGTAGAG CCGGGATTAC GAATACTACC CATTTTACAT GAGAGCCTCA ACAAGCCTCC	AGTAGAATTT CTATACAGAG ACTTGCTCAC CAGTAATAAG CTTTTCGTGA AAAGATTAAG AGTCAACATC ATTACTATCA GAGTGCAGTG CCTCCCGAGT ACGGAGTTTC AGGCGTGAGC AGCAATACTA AAAAGGAAAC AATCTAATTC ACATGAACTA	AGGGGAAAAT GAAAATTAAT AGCCATTACG TTCAGTTTCC AGTCTCAGGC CCCTAACTTC TTATTATTAT GCACAATCTC AAGCTGGGAA ACCGTGGTCT CACCGCGCCC ATTTATTAAT TAAGCTCATT AGTTCTACCT TAAACCCAAT	TAAACGTGGA TTTTATCCTT TCTTAGCCAT AGCTATGTTC TCTACTGTAA TTTACAGACT TGGACTAGAA TATTTTATTT
40	GTCAGAATAA CTCCAGGAGG ATTGTAAAGG CTCTCATACT AATGGAGATA GAGCTAGCTG TAATGTCTGG TTTTTTTTTT	CAAGAAGACA GAGAAATGAG TCGI'GTGACT AACI'ATGCCT ATCAGAATCC GGCCCTCCTG TACAAAGTAA AGATGAGTC TCCI GGGTTC CCCGGCTAAT CACCTTGGCC ACTACTACTA TCAC AAGAAT TGGCATACAT CTCC TCCATC ACCI AAGCAA	ACCAAGCATT CAGTGGCCTG TTTAGCCTTT CCTTGGTCAT CCCACTCATT ACTGTTATAA GCACCCAATA TGGCTCTGTC ATGCCATTCT TTTTTGTATT TCCCAAAGTG CTACCTATAT CCTACCTTCT CTGTAAGTGG CCTTTACTGT TAACGCATGT	AAGTAGGGAC AGTCTGGTAA AATCGAGAAAG GTTACATAAT GGATTGTTGT AGATTAAATG AATGTTAGCT ACCCAGGCTG CCTGCCTCAG TTTAGTAGAG CCGGGATTAC GAATACTACC CATTTTACAT GAGAGCCTCA ACAAGCCTCC TCACCTAGAA	AGTAGAATTT CTATACAGAG ACTTGCTCAC CAGTAATAAG CTTTTCGTGA AAAGATTAAG AGTCAACATC ATTACTATCA GAGTGCAGTG CCTCCCGAGT ACGGAGTTTC AGGCGTGAGC AGCAATACTA AAAAGGAAAC AATCTAATTC ACATGAACTA GGTTTTAAAA	AGGGGAAAAT GAAAATTAAT AGCCATTACG TTCAGTTTCC AGTCTCAGGC CCCTAACTTC TTATTATTAT GCACAATCTC AAGCTGGGAA ACCGTGGTCT CACCGCGCCC ATTTATTATAT TAAGCTCATT AGTTCTACCT TAAACCCAAT TGTAACAAAA	TAAACGTGGA TTTTATCCTT TCTTAGCCAT AGCTATGTTC TCTACTGTAA TTTACAGACT TGGACTAGAA TATTTTATTT
40	GTCAGAATAA CTCCAGGAGG ATTGTAAAGG CTCTCATACT AATGGAGATA GAGCTAGCTG TAATGTCTGG TTTTTTTTTT	CAAGAAGACA GAGAAATGAG TCGI'GTGACT AACI'ATGCCT ATCAGAATCC GGCCCTCCTG TACAAAGTAA AGATGAGTC TCCI GGGTTC CCCGGCTAAT CACCTTGGCC ACTACTACTA TCAC AAGAAT TGGCATACAT CTCC TCCATC ACCI AAGCAA TCAC'AATCGTC	ACCAAGCATT CAGTGGCCTG TTTAGCCTTT CCTTGGTCAT CCCACTCATT ACTGTTATAA GCACCCAATA TGGCTCTGTC ATGCCATTCT TTTTTGTATT TCCCAAAGTG CTACCTATAT CCTACCTTCT CTGTAAGTGG CCTTTACTGT TAACGCATGT AGTGAGAGTT	AAGTAGGGAC AGTCTGGTAA AATCGAGAAAG GTTACATAAT GGATTGTTGT AGATTAAATG AATGTTAGCT ACCCAGGCTG CCTGCCTCAG TTTAGTAGAG CCGGGATTAC GAATACTACC CATTTTACAT GAGAGCCTCA ACAAGCCTCC TCACCTAGAA TACTACTGCC	AGTAGAATTT CTATACAGAG ACTTGCTCAC CAGTAATAAG CTTTTCGTGA AAAGATTAAG AGTCAACATC ATTACTATCA GAGTGCAGTG CCTCCCGAGT ACGGAGTTTC AGGCGTGAGC AGCAATACTA AAAAGGAAAC AATCTAATTC ACATGAACTA GGTTTTAAAA AGCACTATGG	AGGGGAAAAT GAAAATTAAT AGCACTTACG TTCAGTTTCC AGTCTCAGGC CCCTAACTTC TTATTATTAT GCACAATCTC AAGCTGGGAA ACCGTGGTCT CACCGCGCCC ATTTATTATTAT TAAGCTCATT AGTTCTACCT TAAACCCAAT TGTAACAAAA TATGTTTCCT	TAAACGTGGA TTTTATCCTT TCTTAGCCAT AGCTATGTTC TCTACTGTAA TTTACAGACT TGGACTAGAA TATTTTATTT
40	GTCAGAATAA CTCCAGGAGG ATTGTAAAGG CTCTCATACT AATGGAGATA GAGCTAGCTG TAATGTCTGG TTTTTTTTTT	CAAGAAGACA GAGAAATGAG TCGI'GTGACT AACI'ATGCCT ATCAGAATCC GGCCCTCCTG TACAAAGTAA AGATGAGTC TCCI GGGTTC CCCGGCTAAT CACCTTGGCC ACTACTACTA TCAC AAGAAT TGGCATACAT CTCC TCCATC ACCI AAGCAA TCAC AAGCAA TCAC AAGCAA TCAC AAGCAA TCAC AAGCAA TCAC AACCATC ACCI AAGCAA TCAC AACCATC TCACTACATC	ACCAAGCATT CAGTGGCCTG TTTAGCCTTT CCTTGGTCAT CCCACTCATT ACTGTTATAA GCACCCAATA TGGCTCTGTC ATGCCATTCT TTTTTGTATT TCCCAAAGTG CTACCTATAT CCTACCTTCT CTGTAAGTGG CCTTTACTGT TAACGCATGT AGTGAGAGTT TGAACAAATA	AAGTAGGGAC AGTCTGGTAA AATCGAGAAAG GTTACATAAT GGATTGTTGT AGATTAAATG AATGTTAAGCT ACCCAGGCTG CCTGCCTCAG TTTAGTAGAG CCGGGATTAC GAATACTACC CATTTTACAT GAGAGCCTCA ACAAGCCTCC TCACCTAGAA TACTACTGCC TGTCTAACAT	AGTAGAATTT CTATACAGAG ACTTGCTCAC CAGTAATAAG CTTTTCGTGA AAAGATTAAG AGTCAACATC ATTACTATCA GAGTGCAGTG CCTCCCGAGT ACGGAGTTTC AGGCGTGAGC AGCAATACTA AAAAGGAAAC AATCTAATTC ACATGAACTA GGTTTTAAAA AGCACTATGG CAAGACCACA	AGGGGAAAAT GAAAATTAAT AGCCATTACG TTCAGTTTCC AGTCTCAGGC CCCTAACTTC TTATTATTAT GCACAATCTC AAGCTGGGAA ACCGTGGTCT CACCGCGCCC ATTTATTAAT TAAGCTCATT AGTTCTACCT TAAACCCAAT TGTAACAAAA TATGTTTCCT CTATTTACAA	TAAACGTGGA TTTTATCCTT TCTTAGCCAT AGCTATGTTC TCTACTGTAA TTTACAGACT TGGACTAGAA TATTTTATTT
40	GTCAGAATAA CTCCAGGAGG ATTGTAAAGG CTCTCATACT AATGGAGATA GAGCTAGCTG TAATGTCTGG TTTTTTTTTG AAGCTCTGCC CGCCACTGTT GTGATCCACC TATTATTATT TGTCTAAACC AACTGCCCAA ATCATGGTTT TTAAGATAAT TAAAAATCAC GCTATACACA AGCTTTTCTT	CAAGAAGACA GAGAAATGAG TCGI'GTGACT AACI'ATGCCT ATCAGAATCC GGCCCTCCTG TACAAAGTAA AGAT GAGTC TCCI GGGTTC CCCGGCTAAT CACCTTGGCC ACTACTACTA TCAC AAGAAT TGGCATACAT CTCC TCCATC ACCI AAGCAA TCAC'ATCGTC TCACTACTAC TCACTACTAC ACCI AAGCAA TCAC'ATCGTC TACCTACATG ACTTACATG	ACCAAGCATT CAGTGGCCTG TTTAGCCTTT CCTTGGTCAT CCCACTCATT ACTGTTATAA GCACCCAATA TGGCTCTGTC ATGCCATTCT TTTTTGTATT TCCCAAAGTG CTACCTATAT CCTACCTTCT CTGTAAGTGG CCTTTACTGT TAACGCATGT AGTGAGAGTT TGAACAAATA GTATTGAGGA	AAGTAGGGAC AGTCTGGTAA AATCGAGAAAG GTTACATAAT GGATTGTTGT AGATTAAATG AATGTTAGCT ACCCAGGCTG CCTGCCTCAG TTTAGTAGAG CCGGGATTAC GAATACTACC CATTTTACAT GAGAGCCTCA ACAAGCCTCC TCACCTAGAA TACTACTGCC TGTCTAACAT CATTTTAGAG	AGTAGAATTT CTATACAGAG ACTTGCTCAC CAGTAATAAG CTTTTCGTGA AAAGATTAAG AGTCAACATC ATTACTATCA GAGTGCAGTG CCTCCCGAGT ACGGAGTTTC AGGCGTGAGC AGCAATACTA AAAAGGAAAC AATCTAATTC ACATGAACTA GGTTTTAAAA AGCACTATGG CAAGACCACA TGCCCGTTTT	AGGGGAAAAT GAAAATTAAT AGCCATTACT ACCACTTACG TTCAGTTTCC AGTCTCAGGC CCCTAACTTC TTATTATTAT GCACAATCTC AAGCTGGGAA ACCGTGGTCT CACCGCGCCC ATTTATTAAT TAAGCTCATT AGTTCTACCT TAAACCCAAT TGTAACAAAA TATGTTTCCT CTATTTACAA TCACCATTAT	TAAACGTGGA TTTTATCCTT TCTTAGCCAT AGCTATGTTC TCTACTGTAA TTTACAGACT TGGACTAGAA TATTTATTT GGCTCACTGC TACAGGCACC CCATCTCCTC GGCCTATTAT GACTGGATTA GAGTAAAAAA ATTCCTGTTT TATAAGAAAA TAAAATCTTT CTTTATATCC AAGCAATGCA
40	GTCAGAATAA CTCCAGGAGG ATTGTAAAGG CTCTCATACT AATGGAGATA GAGCTAGCTG TAATGTCTGG TTTTTTTTTG AAGCTCTGCC CGCCACTGTT GTGATCCACC TATTATTATT TGTCTAAACC AACTGCCCAA ATCATGGTTT TTAAGATAAT TAAAAATCAC GCTATACACA AGCTTTTCTT ACAATGAACA	CAAGAAGACA GAGAAATGAG TCGI'GTGACT AACI'ATGCCT ATCAGAATCC GGC'CTCCTG TACAAAGTAA AGAT GGGTTC CCCGGCTAAT CACCTTGGCC ACTACTACTA TCAC AAGAAT TCGCATCACT ACCI AAGCAA TCAC TACGTC TCCTTCCATC ACCI AAGCAA TCAC TACGTC TACCTACATG ACTTACATG ACTTACATG ACTTAGCAAT TCTGTTATAAA	ACCAAGCATT CAGTGGCCTG TTTAGCCTTT CCTTGGTCAT CCCACTCATT ACTGTTATAA GCACCCAATA TGGCTCTGTC ATGCCATTCT TTTTTGTATT TCCCAAAGTG CTACCTATAT CCTACCTTCT CTGTAAGTGG CCTTTACTGT TAACGCATGT AGTGAGAGTT TGAACAAATA GTATTGAGGA TAAATATTCA	AAGTAGGGAC AGTCTGGTAA AATCGAGAAAG GTTACATAAT GGATTGTTGT AGATTAAATG AATGTTAGCT ACCCAGGCTG CCTGCCTCAG TTTAGTAGAG CCGGGATTAC GAATACTACC CATTTTACAT GAGAGCCTCA ACAAGCCTCC TCACCTAGAA TACTACTGCC TGTCTAACAT CATTTTAGAG TTTCTCCAC	AGTAGAATTT CTATACAGAG ACTTGCTCAC CAGTAATAAG CTTTTCGTGA AAAGATTAAG AGTCAACATC ATTACTATCA GAGTGCAGTG CCTCCCGAGT ACGGAGTTTC AGGCGTGAGC AGCAATACTA AAAAGGAAAC AATCTAATTC ACATGAACTA GGTTTTAAAA AGCACTATGG CAAGACCACA TGCCCGTTTT CCTTTATTTC	AGGGGAAAAT GAAAATTAAT AGCCATTACG TTCAGTTTCC AGTCTCAGGC CCCTAACTTC TTATTATTAT GCACAATCTC AAGCTGGGAA ACCGTGGTCT CACCGCGCCC ATTTATTAAT TAAGCTCATT AGTTCTACCT TAAACCCAAT TGTAACAAAA TATGTTTCCT CTATTTACAA TCACCATTAT CTTAGAATAT	TAAACGTGGA TTTTATCCTT TCTTAGCCAT AGCTATGTTC TCTACTGTAA TTTACAGACT TGGACTAGAA TATTTATTT GGCTCACTGC TACAGGCACC CCATCTCCTC GGCCTATTAT GACTGGATTA GAGTAAAAA ATTCCTGTTT TATAAGAAAA TAAAATCTTT CTTTATATCC AAGCAATGCA ATTCCTAGAA
40	GTCAGAATAA CTCCAGGAGG ATTGTAAAGG CTCTCATACT AATGGAGATA GAGCTAGCTG TAATGTCTGG TTTTTTTTTG AAGCTCTGCC CGCCACTGTT GTGATCCACC TATTATTATT TGTCTAAACC AACTGCCCAA ATCATGGTTT TTAAGATAAT TAAAAATCAC GCTATACACA AGCTTTTCTT ACAATGAACA GTAGAACTTC	CAAGAAGACA GAGAAATGAG TCGI'GTGACT AACI'ATGCCT ATCAGAATCC GGC'CTCCTG TACAAAGTAA AGAT GGGTTC CCCGGCTAAT CACCTTGGCC ACTACTACTA TCAC AAGAAT TCGCATCACT ACCI AAGCAA TCAC'AAGCAA TCAC'AAGCAA TCAC'AAGCAA TCAC'AAGCAA TCAC'AAGCAA TCAC'AAGCAA TCAC'TACATG ACTTAGCAAT TCTGTATAAA CCAGAGCCAT	ACCAAGCATT CAGTGGCCTG TTTAGCCTTT CCTTGGTCAT CCCACTCATT ACTGTTATAA GCACCCAATA TGGCTCTGTC ATGCCATTCT TTTTTGTATT TCCCAAAGTG CTACCTATAT CCTACCTTCT CTGTAAGTGG CCTTTACTGT TAACGCATGT AGTGAGAGTT TGAACAAATA GTATTGAGGA TAAATATTCA GAGGATTTGT	AAGTAGGGAC AGTCTGGTAA AATCGAGAAAG GTTACATAAT GGATTGTTGT AGATTAAATG AATGTTAGCT ACCCAGGCTG CCTGCCTCAG TTTAGTAGAG CCGGGATTAC GAATACTACC CATTTTACAT GAGAGCCTCA ACAAGCCTCC TCACCTAGAA TACTACTGCC TGTCTAACAT CATTTTAGAG TTTCTCTCAC GACGCTATTG	AGTAGAATTT CTATACAGAG ACTTGCTCAC CAGTAATAAG CTTTTCGTGA AAAGATTAAG AGTCAACATC ATTACTATCA GAGTGCAGTG CCTCCCGAGT ACGGAGTTTC AGGCGTGAGC AGCAATACTA AAAAGGAAAC AATCTAATTC ACATGAACTA GGTTTTAAAA AGCACTATGG CAAGACCACA TGCCCGTTTT CCTTTATTTC ATATGTGCCA	AGGGGAAAAT GAAAATTAAT AGCCATTACG TTCAGTTTCC AGTCTCAGGC CCCTAACTTC TTATTATTAT GCACAATCTC AAGCTGGGAA ACCGTGGTCT CACCGCGCCC ATTTATTAAT TAAGCTCATT AGTTCTACCT TAAACCCAAT TGTAACAAAA TATGTTTCCT CTATTTACA TCACCATTAT CTTAGAATAT CTTTAGAATAT	TAAACGTGGA TTTTATCCTT TCTTAGCCAT AGCTATGTTC TCTACTGTAA TTTACAGACT TGGACTAGAA TATTTATTT GGCTCACTGC TACAGGCACC CCATCTCCTC GGCCTATTAT GACTGGATTA GAGTAAAAAA ATTCCTGTTT TATAAGAAAA TAAAATCTTT CTTTATATCC AAGCAATGCA ATTCCTAGAA TCTGTGACAT
40 45 50	GTCAGAATAA CTCCAGGAGG ATTGTAAAGG CTCTCATACT AATGGAGATA GAGCTAGCTG TAATGTCTGG TTTTTTTTTG AAGCTCTGCC CGCCACTGTT GTGATCCACC TATTATTATT TGTCTAAACC AACTGCCCAA ATCATGGTTT TTAAGATAAT TAAAAATCAC GCTATACACA AGCTTTTCTT ACAATGAACA GTAGAACTTC ATATAATTAT	CAAGAAGACA GAGAAATGAG TCGI'GTGACT AACI'ATGCCT ATCAGAATCC GGC'CTCCTG TACAAAGTAA AGAT GAGTTC CCCGGCTAAT CACCTTGGCC ACTACTACTA TCAC AAGAAT TCGC'ATACAT CACCI TCCATC ACCI AAGCAA TCA' ATCGTC TACCTACAT ACCTACAT ACCTACAT ACCTACAT TCTGTCATC ACCTACAT TCTGTATAAA CCAGAGCCAT TTTTTATAAACCA	ACCAAGCATT CAGTGGCCTG TTTAGCCTTT CCTTGGTCAT CCCACTCATT ACTGTTATAA GCACCCAATA TGGCTCTGTC ATGCCATTCT TTTTTGTATT TCCCAAAGTG CTACCTATAT CCTACCTTCT CTGTAAGTGG CCTTTACTGT TAACGCATGT AGTGAGAGTT TGAACAAATA GTATTGAGGA TAAATATTCA GAGGATTTGT TTCATTTTTT	AAGTAGGGAC AGTCTGGTAA AATCGAGAAAG GTTACATAAT GGATTGTTGT AGATTAAATG AATGTTAGCT ACCCAGGCTG CCTGCCTCAG TTTAGTAGAG CCGGGATTAC GAATACTACC CATTTTACAT GAGAGCCTCA ACAAGCCTCC TCACCTAGAA TACTACTGCC TGTCTAACAT CATTTTAGAG TTTCTCAC GACGCTATTG TCTCACAGAGTG	AGTAGAATTT CTATACAGAG ACTTGCTCAC CAGTAATAAG CTTTTCGTGA AAAGATTAAG AGTCAACATC ATTACTATCA GAGTGCAGTG CCTCCCGAGT ACGGAGTTTC AGGCGTGAGC AGCAATACTA AAAAGGAAAC AATCTAATTC ACATGAACTA GGTTTTAAAA AGCACTATGG CAAGACCACA TGCCCGTTTT CCTTTATTTC ATATGTGCCA CATTGGTTTG	AGGGGAAAAT GAAAATTAAT AGCCATTACG TTCAGTTTCC AGTCTCAGGC CCCTAACTTC TTATTATTAT GCACAATCTC AAGCTGGGAA ACCGTGGTCT CACCGCGCCC ATTTATTAAT TAAGCTCATT AGTTCTACCT TAAACCCAAT TGTAACAAAA TATGTTTCCT CTATTTACA TCACCATTAT CTTAGAATAT CTTTAGAATAT CTTTGCACTC AAAACATAGA	TAAACGTGGA TTTTATCCTT TCTTAGCCAT AGCTATGTTC TCTACTGTAA TTTACAGACT TGGACTAGAA TATTTATTT GGCTCACTGC TACAGGCACC CCATCTCCTC GGCCTATTAT GACTGGATTA GAGTAAAAAA ATTCCTGTTT TATAAGAAAA TAAAATCTTT CTTTATATCC AAGCAATGCA ATTCCTAGAA TCTGTGACAT CGGGAAATAC
40	GTCAGAATAA CTCCAGGAGG ATTGTAAAGG CTCTCATACT AATGGAGATA GAGCTAGCTG TTATTTTTTG AAGCTCTGCC CGCACTGTT GTGATCCACC TATTATTATT TGTCTAAACC AACTGCCAA ATCATGGTTT TTAAGATAAT TAAAAATCAC GCTATACACA AGCTTTTCTT ACAATGAACA GTAGAATTTC ATATAATTT TGGTAGACCT TTAAGATAAT TAAAATTAT TACAATGAACA GTAGAATTTC ATATAATTAT TGGTAGTCTT	CAAGAAGACA GAGAATGAG TCGI'GTGACT AACI'ATGCCT ATCAGAATCC GGC'CTCCTG TACAAAGTAA AGAT GAGTC TCCI GGGTTC CCCGGCTAAT CACCTTGGCC ACTACTACTA TCAC AAGAAT TGGCATACAT CTCC TCCATC ACCI AAGCAA TCA' ATCGTC TACCTACAT ACTTAGCAAT TCTGTCATC ACTTAGCAAT TCTGTTATAAA CCAGAGCCAT TTTTATAATGCA CCTTGTCAGT	ACCAAGCATT CAGTGGCCTG TTTAGCCTTT CCTTGGTCAT CCCACTCATT ACTGTTATAA GCACCCAATA TGGCTCTGTC ATGCCATTCT TTTTTGTATT TCCCAAAGTG CTACCTATAT CCTACCTTCT CTGTAAGTGG CCTTTACTGT TAACGCATGT AGTGAGAGTT TGAACAAATA GTATTGAGGA TAAATATTCA GAGGATTTGT TTCATTTTTT TAGAAACACC	AAGTAGGGAC AGTCTGGTAA AATCGAGAAAG GTTACATAAT GGATTGTTGT AGATTAAATG AATGTTAGCT ACCCAGGCTG CCTGCCTCAG TTTAGTAGAG CCGGGATTAC GAATACTACC CATTTTACAT GAGAGCCTCA ACAAGCCTCC TCACCTAGAA TACTACTGCC TGTCTAACAT CATTTTAGAG TTTCTCTCAC GACGCTATTG TCTCACAGAGTG CAAACAATGA	AGTAGAATTT CTATACAGAG ACTTGCTCAC CAGTAATAAG CTTTTCGTGA AAAGATTAAG AGTCAACATC ATTACTATCA GAGTGCAGTG CCTCCCGAGT ACGGAGTTTC AGGCGTGAGC AGCAATACTA AAAAGGAAAC AATCTAATTC ACATGAACTA GGTTTTAAAA AGCACTATGG CAAGACCACA TGCCCGTTTT CCTTTATTTC ATATGTGCCA CATTCGTTTG AAAATGAAAA	AGGGGAAAAT GAAAATTAAT AGCCATTACG TTCAGTTTCC AGTCTCAGGC CCCTAACTTC TTATTATTAT GCACAATCTC AAGCTGGGAA ACCGTGGTCT CACCGCGCCC ATTTATTAAT TAAGCTCATT AGTTCTACCT TAAACCCAAT TGTAACAAAA TATGTTTCCT CTATTTACA TCACCATTAT CTTAGAATAT CTTTGCACTC AAAACATAGA AGTTGCACAA	TAAACGTGGA TTTTATCCTT TCTTAGCCAT AGCTATGTTC TCTACTGTAA TTTACAGACT TGGACTAGAA TATTTATTT GGCTCACTGC TACAGGCACC CCATCTCCTC GGCCTATTAT GACTGGATTA GAGTAAAAA ATTCCTGTTT TATAAGAAAA ATTCCTGTTT CTTTATATCC AAGCAATGCA ATTCCTAGAA TCTGTGACAT CGGGAAATAC ATAGTCTCTA
40 45 50	GTCAGAATAA CTCCAGGAGG ATTGTAAAGG CTCTCATACT AATGGAGATA GAGCTAGCTG TAATGTCTGG TTTTTTTTTT	CAAGAAGACA GAGAATGAG TCGI'GTGACT AACI'ATGCCT ATCAGAATCC GGC'CTCCTG TACAAAGTAA AGAT'GAGTC TCCI GGGTTC CCCGGCTAAT CACCTTGGCC ACTACTACTA TCAC AAGAAT TGGC'ATACAT CTCC TCCATC ACCI AAGCAA TCA' ATCGTC TACCTACAT ACCTTACAT ACTTAGCAAT TCTGTTATAAA CCAGAGCCAT TTTTAATGCA CCTTGTCAGT AAC' ATTGCC	ACCAAGCATT CAGTGGCCTG TTTAGCCTTT CCTTGGTCAT CCCACTCATT ACTGTTATAA GCACCCAATA TGGCTCTGTC ATGCCATTCT TTTTTGTATT TCCCAAAGTG CTACCTACT CTGTAAGTGG CCTTTACTGT TAACGCATGT AGTGAGAGTT TGAACAAATA GTATTGAGGA TAAATATCA GAGGATTTGT TTCATTTTT TAGAAACACC TGAGGAATTG	AAGTAGGGAC AGTCTGGTAA AATCGAGAAAG GTTACATAAT GGATTGTTGT AGATTAAATG AATGTTAGCT ACCCAGGCTG CCTGCCTCAG TTTAGTAGAG CCGGGATTAC GAATACTACC CATTTTACAT GAGAGCCTCA ACAAGCCTCC TCACCTAGAA TACTACTGCC TGTCTAACAT CATTTTAGAG TTTCTCTCAC GACGCTATTG TCTCACAGAGTG CAAACAATGA AAGTTTAAAA	AGTAGAATTT CTATACAGAG ACTTGCTCAC CAGTAATAAG CTTTTCGTGA AAAGATTAAG AGTCAACATC ATTACTATCA GAGTGCAGTG CCTCCCGAGT ACGGAGTTTC AGGCGTGAGC AGCAATACTA AAAAGGAAAC AATCTAATTC ACATGAACTA GGTTTTAAAA AGCACTATGG CAAGACCACA TGCCCGTTTT CCTTTATTTC ATATGTGCCA CATTCGTTTG AAAATGAAAA AGAAGCACAT	AGGGGAAAAT GAAAATTAAT AGCCATTACG TTCAGTTTCC AGTCTCAGGC CCCTAACTTC TTATTATTAT GCACAATCTC AAGCTGGGAA ACCGTGGTCT CACCGCGCCC ATTTATTAAT TAAGCTCATT AGTTCTACCT TAAACCCAAT TGTAACAAAA TATGTTTCCT CTATTTACA TCACCATTAT CTTAGAATAT CTTTGCACTC AAACATAGA AGTTGCACAA AGCACAACAAC	TAAACGTGGA TTTTATCCTT TCTTAGCCAT AGCTATGTTC TCTACTGTAA TTTACAGACT TGGACTAGAA TATTTATTT GGCTCACTGC TACAGGCACC CCATCTCCTC GGCCTATTAT GACTGGATTA GAGTAAAAAA ATTCCTGTTT TATAAGAAAA TAAAATCTTT CTTTATATCC AAGCAATGCA ATTCCTAGAA TCTGTGACAT CGGGAAATAC ATAGTCTCTA AAGGATAATC
40 45 50	GTCAGAATAA CTCCAGGAGG ATTGTAAAGG CTCTCATACT AATGGAGATA GAGCTAGCTG TAATGTCTGG TTTTTTTTTG AAGCTCTGCC CGCCACTGTT GTGATCCACC TATTATTATT TGTCTAAACC AACTGCCAA ATCATGGTTT TAAGATAAT TAAAAATCAC GCTATACACA AGCTTTCTT ACAATGAACA GTAGAATTC ATATAATTAT TGGTAGTCTT AAAACAATGA CTAGAAAACC CTAGAAAACC	CAAGAAGACA GAGAATGAG TCGTGTGACT AACTATGCCT ATCAGAATCC GGCCCTCCTG TACAAAGTAA AGATGAGTC CCCGGCTAAT CACCTTGGCC ACTACTACTA TCAC AAGAAT TGGCATACAT CACCTACAT CACCTACAT CACCTACAT CACCTACAT CTCCTCCATC ACCTACAT CTCCTCCATC ACCTACAT CTCTTACAT CTCTTACAT CTCTTACAT CTCTTTATAAA CCAGAGCCAT TTTTAATGCA CCTTGTCAGT AACTATTGCC AGTTCTGCTG	ACCAAGCATT CAGTGGCCTG TTTAGCCTTT CCTTGGTCAT CCCACTCATT ACTGTTATAA GCACCCAATA TGGCTCTGTC ATGCCATTCT TTTTTGTATT TCCCAAAGTG CTACCTACT CTGTAAGTGG CCTTTACTGT TAACGCATGT AGTGAGAGTT TGAACAAATA GTATTGAGGA TAAATATCA GAGGATTTGT TTCATTTTT TAGAAACACC TGAGGAATTG ACTGGGTGAT	AAGTAGGGAC AGTCTGGTAA AATCGAGAAAG GTTACATAAT GGATTGTTGT AGATTAAATG AATGTTAGCT ACCCAGGCTG CCTGCCTCAG TTTAGTAGAG CCGGGATTAC GAATACTACC CATTTTACAT GAGAGCCTCA ACAAGCCTCC TCACCTAGAA TACTACTGCC TGTCTAACAT CATTTTAGAG TTTCTCTCAC GACGCTATTG TCTCACAGAGTG CAAACAATGA AAGTTTAAAA TTCACTTCTC	AGTAGAATTT CTATACAGAG ACTTGCTCAC CAGTAATAAG CTTTTCGTGA AAAGATTAAG AGTCAACATC ATTACTATCA GAGTGCAGTG CCTCCCGAGT ACGGAGTTTC AGGCGTGAGC AGCAATACTA AAAAGGAAAC AATCTAATTC ACATGAACTA GGTTTTAAAA AGCACTATGG CAAGACCACA TGCCCGTTTT CCTTTATTTC ATATGTGCCA CATTCGTTTG AAAATGAAAA AGAAGCACAT TTTGCTTCCT	AGGGGAAAAT GAAAATTAAT AGCCATTACG TTCAGTTTCC AGTCTCAGGC CCCTAACTTC TTATTATTAT GCACAATCTC AAGCTGGGAA ACCGTGGTCT CACCGCGCCC ATTTATTAAT TAAGCTCATT AGTTCTACCT TAAACCCAAT TGTAACAAAA TATGTTTCCT CTATTTACA TCACCATTAT CTTAGAATAT CTTTGCACTC AAACATAGA AGTTGCACAA AGCACAAC CATCTGGATT	TAAACGTGGA TTTTATCCTT TCTTAGCCAT AGCTATGTTC TCTACTGTAA TTTACAGACT TGGACTAGAA TATTTATTT GGCTCACTGC TACAGGCACC CCATCTCCTC GGCCTATTAT GACTGGATTA GAGTAAAAA ATTCCTGTTT TATAAGAAAA ATTCCTGTTT CTTTATATCC AAGCAATGCA ATTCCTAGAA TCTGTGACAT CGGGAAATAC ATAGTCTCTA AAGGATAATC GGAATATTCC GGAATATCC GGAATATCC
40 45 50	GTCAGAATAA CTCCAGGAGG ATTGTAAAGG CTCTCATACT AATGGAGATA GAGCTAGCTG TAATGTCTGG TTTTTTTTTT	CAAGAAGACA GAGAATGAG TCGTGTGACT AACTATGCCT ATCAGAATCC GGCCCTCCTG TACAAAGTAA AGATGAGTC CCCGGCTAAT CACCTTGGCC ACTACTACTA TCAC AAGAAT TGGCATACAT CACCTACATC ACCTACATC ACCTACATC ACCTACATC ACCTACATC TCACTACATC ACCTACATC ACCTTGCTC ACCTTGCTG TCCAGAACTA	ACCAAGCATT CAGTGGCCTG TTTAGCCTTT CCTTGGTCAT CCCACTCATT ACTGTTATAA GCACCCAATA TGGCTCTGTC ATGCCATTCT TTTTTGTATT TCCCAAAGTG CTACCTACT CTGTAAGTGG CCTTTACTGT TAACGCATGT AGTGAGAGTT TGAACAAATA GTATTGAGGA TAAATATCA GAGGATTTGT TTCATTTTT TAGAAACACC TGAGGAATTG ACTGGGTGAT TTTTCCCTGT	AAGTAGGGAC AGTCTGGTAA AATCGAGAAAG GTTACATAAT GGATTGTTGT AGATTAAATG AATGTTAGCT ACCCAGGCTG CCTGCCTCAG TTTAGTAGAG CCGGGATTAC GAATACTACC CATTTTACAT GAGAGCCTCA ACAAGCCTCC TCACCTAGAA TACTACTGCC TGTCTAACAT CATTTTAGAG TTTCTCTCAC GACGCTATTG TCTCACAGAGTG CAAACAATGA AAGTTTAAAA TTCACTTCTC TTGTACTAGA	AGTAGAATTT CTATACAGAG ACTTGCTCAC CAGTAATAAG CTTTTCGTGA AAAGATTAACA AGTCAACATC ATTACTATCA GAGTGCAGTG CCTCCCGAGT ACGGAGTTTC AGGCGTGAGC AGCAATACTA AAAAGGAAAC AATCTAATTC ACATGAACTA GGTTTTAAAA AGCACTATGG CAAGACCACA TGCCCGTTTT CCTTTATTTC ATATGTGCCA CATTCGTTTG AAAATGAAAA AGAAGCACAT TTTGCTTCCT CTGTGTATATT	AGGGGAAAAT GAAAATTAAT AGCCATTACG TTCAGTTTCC AGTCTCAGGC CCCTAACTTC TTATTATTAT GCACAATCTC AAGCTGGGAA ACCGTGGTCT CACCGCGCCC ATTTATTAAT TAAGCTCATT AGTTCTACCT TAAACCCAAT TGTAACAAAA TATGTTTCCT CTATTTACA TCACCATTAT CTTAGAATAT CTTTGCACTC AAACATAGA AGTTGCACAA AGCTCGATT CATCTGGATT CATCTGGATT CATCTGGATT CATCTGGATT CATCTGGATT CATCTGGATT CATCTGGATT	TAAACGTGGA TTTTATCCTT TCTTAGCCAT AGCTATGTTC TCTACTGTAA TTTACAGACT TGGACTAGAA TATTTATTT GGCTCACTGC TACAGGCACC CCATCTCCTC GGCCTATTAT GACTGGATTA GAGTAAAAAA ATTCCTGTTT TATAAGAAAA ATTCCTGTTT CTTTATATCC AAGCAATGCA ATTCCTAGAA TCTGTGACAT CGGGAAATAC ATAGTCTCTA AAGGATAATC GGAATATTCC TGTACATAGA
40 45 50	GTCAGAATAA CTCCAGGAGG ATTGTAAAGG CTCTCATACT AATGGAGATA GAGCTAGCTG TAATGTCTGG TTTTTTTTTT	CAAGAAGACA GAGAATGAG TCGTGTGACT AACTATGCCT ATCAGAATCC GGCCCTCCTG TACAAAGTAA AGATGAGTC CCCGGCTAAT CACCTTGGCC ACTACTACTA TCAC AAGAAT TGGCATACAT CACCTACATC ACCTACATC ACCTACATC ACCTACATC ACCTACATC TCACTACATC ACCTACATC ACCTTGTCAGT AACTATTGCC AGTTCTGCTG TCCAGAACTA CACTTGTGAT	ACCAAGCATT CAGTGGCCTG TTTAGCCTTT CCTTGGTCAT CCCACTCATT ACTGTTATAA GCACCCAATA TGGCTCTGTC ATGCCATTCT TTTTTGTATT TCCCAAAGTG CTACCTACT CTGTAAGTGG CCTTTACTGT TAACGCATGT AGTGAGAGTT TGAACAAATA GTATTGAGGA TAAATATCA GAGGATTTGT TCATTTTT TAGAAACACC TGAGGAATTG ACTGGGTGAT TTTTCCCTGT CATGGTTTTA	AAGTAGGGAC AGTCTGGTAA AATCGAGAAAG GTTACATAAT GGATTGTTGT AGATTAAATG AATGTTAGCT ACCCAGGCTG CCTGCCTCAG TTTAGTAGAG CCGGGATTAC GAATACTACC CATTTTACAT GAGAGCCTCA ACAAGCCTCC TCACCTAGAA TACTACTGCC TGTCTAACAT CATTTTAGAG TTTCTCTCAC GACGCTATTG TCTCAGAGTG CAAACAATGA AAGTTTAAAA TTCACTTCTC TTGTACTAGA GAAATCATCA	AGTAGAATTT CTATACAGAG ACTTGCTCAC CAGTAATAAG CTTTTCGTGA AAAGATTAAG AGTCAACATC ATTACTATCA GAGTGCAGTG CCTCCCGAGT ACGGAGTTTC AGGCGTGAGC AGCAATACTA AAAAGGAAAC AATCTAATTC ACATGAACTA GGTTTTAAAA AGCACTATGG CAAGACCACA TGCCCGTTTT CCTTTATTTC ATATGTGCCA CATTCGTTTG AAAATGAAAA AGAAGCACAT TTTGCTTCCT CTGTGTATAT AGCCTAGGTC	AGGGGAAAAT GAAAATTAAT AGCCATTACG TTCAGTTTCC AGTCTCAGGC CCCTAACTTC TTATTATTAT GCACAATCT AAGCTGGGAA ACCGTGGTCT CACCGCGCCC ATTTATTAAT TAAGCTCATT AGTTCTACCT TAAACCCAAT TGTAACAAAA TATGTTTCCT CTATTTACA TCACCATTAT CTTAGAATAT CTTAGAATAT CTTTGCACT AAACATAGA AGTTGCACAA AGCTTGGATT CATCTGGTT ATCACCTTTT CATCTGGTT ATCACCTTTT ATCACACAC CATCTGGATT CATCTGTGTT ATCACCTTTT	TAAACGTGGA TTTTATCCTT TCTTAGCCAT AGCTATGTTC TCTACTGTAA TTTACAGACT TGGACTAGAA TATTTATTT GGCTCACTGC TACAGGCACC CCATCTCCTC GGCCTATTAT GACTGGATTA GAGTAAAAAA ATTCCTGTTT TATAAGAAAA ATTCCTGTTT CTTTATATCC AAGCAATGCA ATTCCTAGAA TCTGTGACAT CGGGAAATAC ATAGTCTCTA AAGGATAATC GGAATATTC TGTACATAGA AGCTTCCTGA AGCTTCCTGA
40 45 50	GTCAGAATAA CTCCAGGAGG ATTGTAAAGG CTCTCATACT AATGGAGATA GAGCTAGCTG TAATGTCTGG TTTTTTTTTT	CAAGAAGACA GAGAATGAG TCGTGTGACT AACTATGCCT ATCAGAATCC GGCCCTCCTG TACAAAGTAA AGATGAGTC CCCGGCTAAT CACCTTGGCC ACTACTACTA TCAC AAGAAT TGGCATACAT CACCTACATC ACCTACATC ACCTACATC ACCTACATC ACCTACATC TCACTACAT CTCCTCCATC ACCTACATC ACCTACATC ACCTACATC ACCTACATC TCTTTACATG ACTTAGCAAT TCTGTTATAAA CCAGAGCCAT TTTTAATGCA CCTTGTCAGT AACTATTGCC AGTTCTGCTG TCCAGAACTA CACTTGTGAT AACTATTGCT ACCTTGTGAT AACTACACTTT	ACCAAGCATT CAGTGGCCTG TTTAGCCTTT CCTTGGTCAT CCCACTCATT ACTGTTATAA GCACCCAATA TGGCTCTGTC ATGCCATTCT TTTTTGTATT TCCCAAAGTG CTACCTACT CTGTAAGTGG CCTTTACTGT TAACGCATGT AGTGAGAGTT TGAACAAATA GTATTGAGGA TAAATATTCA GAGGATTTGT TCATTTTT TAGAAACACC TGAGGAATTG ACTGGGTGAT TTTTCCCTGT CATGGTTTTA ATGAGGATCA	AAGTAGGGAC AGTCTGGTAA AATCGAGAAAG GTTACATAAT GGATTGTTGT AGATTAAATG AATGTTAGCT ACCCAGGCTG CCTGCCTCAG TTTAGTAGAG CCGGGATTAC GAATACTACC CATTTTACAT GAGAGCCTCA ACAAGCCTCC TCACCTAGAA TACTACTGCC TGTCTAACAT CATTTTAGAG TTTCTCTCAC GACGCTATTG TCTCAGAGTG CAAACAATGA AAGTTTAAAA TTCACTTCTC TTGTACTAGA GAAATCATCA CATACTACTAC CATTTTAGAG TTTCTCTCAC GACGCTATTG TCTCAGAGTG CAAACAATGA AAGTTTAAAA TTCACTTCTC TTGTACTAGA GAAATCATCA TCAAATACGA	AGTAGAATTT CTATACAGAG ACTTGCTCAC CAGTAATAAG CTTTTCGTGA AAAGATTAAG AGTCAACATC ATTACTATCA GAGTGCAGTG CCTCCCGAGT ACGGAGTTTC AGGCGTGAGC AGCAATACTA AAAAGGAAAC AATCTAATTC ACATGAACTA GGTTTTAAAA AGCACTATGG CAAGACCACA TGCCCGTTTT CCTTTATTTC ATATGTGCCA CATTCGTTTG AAAATGAAAA AGAAGCACAT TTTGCTTCCT CTGTGTATAT AGCCTAGGTC ATTCATCCTG	AGGGGAAAAT GAAAATTAAT AGCCATTACG TTCAGTTTCC AGTCTCAGGC CCCTAACTTC TTATTATTAT GCACAATCT AAGCTGGGAA ACCGTGGTCT CACCGCGCCC ATTTATTAAT TAAGCTCATT AGTTCTACCT TAAACCCAAT TGTAACAAAA TATGTTTCCT CTATTTACA TCACCATTAT CTTAGAATAT CTTAGAATAT CTTTGCACT AAACATAGA AGTTGCACAA AGCTCGTTT ACTTGCACT CACCTTTT CACCTTTT CATCTGCATT CATCTGGATT CATCTGGTTT ATCACCTTTT ATCACCTCTTT ATCACCTTTT ATCACCTCTTT ATCACCTCTT ATCACCTCTT ATCACCTCTT ATCACCTCTT ATCACCTCT ATCACCT	TAAACGTGGA TTTTATCCTT TCTTAGCCAT AGCTATGTTC TCTACTGTAA TTTACAGACT TGGACTAGAA TATTTATTT GGCTCACTGC TACAGGCACC CCATCTCCTC GGCCTATTAT GACTGGATTA GAGTAAAAAA ATTCCTGTTT TATAAGAAAA ATTCCTGTTT CTTTATATCC AAGCAATGCA ATTCCTAGAA TCTGTGACAT CGGGAAATAC ATAGTCTCTA AAGGATAATC GGAATATTCC TGTACATAGA ACCTTCCTGA ACCTTCCTGA ACCTTCCTGA TCAATCAAAG TCAATCAAAG
40 45 50	GTCAGAATAA CTCCAGGAGG ATTGTAAAGG CTCTCATACT AATGGAGATA GAGCTAGCTG TAATGTCTGG TTTTTTTTTT	CAAGAAGACA GAGAATGAG TCGIGTGACT AACI'ATGCCT ATCAGAATCC GGCCCTCCTG TACAAAGTAA AGATGAGTC CCCGGCTAAT CACCTTGGCC ACTACTACTA TCAC AAGAAT TGGCATACAT CTCC TCCATC ACCI AGCAAT CTCC TCCATC ACCI AGCAAT TCTCTACATG ACTTACATG ACTTAGCAAT TCTGTATAAA CCAGAGCCAT TTTTAATGCA CCTTGTCAGT AAC'ATTGCC AGTTCTGCTG TCCAGGACTA CACITGTGAT AAC'ATTGCC AGTTCTGCTG TCCAGAACTA CACITGTGAT ATCAAACTTT GCCAATGATC	ACCAAGCATT CAGTGGCCTG TTTAGCCTTT CCTTGGTCAT CCCACTCATT ACTGTTATAA GCACCCAATA TGGCTCTGTC ATGCCATTCT TTTTTGTATT TCCCAAAGTG CTACCTACT CTGTAAGTGG CCTTTACTGT TAACGCATGT AGTGAGAGTT TGAACAAATA GTATTGAGGA TAAATATTCA GAGGATTTGT TCATTTTT TAGAAACACC TGAGGAATTG ACTGGGTGAT TTTTCCCTGT ACTGGGTGAT TTTTCCCTGT CATGGTTTTA ATGAGGATCA AGTACCTCAC	AAGTAGGGAC AGTCTGGTAA AATCGAGAAAG GTTACATAAT GGATTGTTGT AGATTAAATG AATGTTAGCT ACCCAGGCTG CCTGCCTCAG TTTAGTAGAG CCGGGATTAC GAATACTACC CATTTTACAT GAGAGCCTCA ACAAGCCTCC TCACCTAGAA TACTACTGCC TGTCTAACAT CATTTTAGAG TTTCTCTCAC GACGCTATTG TCTCAGAGTG CAAACAATGA AAGTTTAAAA TTCACTTCTC TTGTACTAGA GAAATCATCA CATACTACAG CAAACAATGA AAGTTTAAAA TTCACTTCTC TTGTACTAGA GAAATCATCA TCAAATACGA GGCTGCTGCA	AGTAGAATTT CTATACAGAG ACTTGCTCAC CAGTAATAAG CTTTTCGTGA AAAGATTAAG AGTCAACATC ATTACTATCA GAGTGCAGTG CCTCCCGAGT ACGGAGTTTC AGGCGTGAGC AGCAATACTA AAAAGGAAAC AATCTAATTC ACATGAACTA GGTTTTAAAA AGCACTATGG CAAGACCACA TGCCCGTTTT CCTTTATTTC ATATGTGCCA CATTCGTTTG AAAATGAAAA AGAAGCACAT TTTGCTTCCT CTGTGTATAT AGCCTAGGTC	AGGGGAAAAT GAAAATTAAT AGCCATTATT ACCACTTACG TTCAGTTTCC AGTCTCAGGC CCCTAACTTC TTATTATTAT GCACAATCT AAGCTGGGAA ACCGTGGTCT CACCGCGCCC ATTTATTAAT TAAGCTCATT AGTTCTACCT TAAACCCAAT TGTAACAAAA TATGTTTCCT CTATTTACA TCACCATTAT CTTAGAATAT CTTAGAATAT CTTTGCACT AAACATAGA AGTTGCACA AGTTGCACA AGCTCGTTT ATCACTTTT ATCACTTTT ATCACCTTTT ATCACCTTTT ATCACCTTTT ATCACCTTTT ATCACCTTTT ATCACCTTTT ATCACCTTTT ATCACCTTTT ATCACCCTTTT ATCACCCTTTT ATCACCCCTTGGATG	TAAACGTGGA TTTTATCCTT TCTTAGCCAT AGCTATGTTC TCTACTGTAA TTTACAGACT TGGACTAGAA TATTTATTT GGCTCACTGC TACAGGCACC CCATCTCCTC GGCCTATTAT GACTGGATTA GAGTAAAAAA ATTCCTGTTT TATAAGAAAA ATTCCTGTTT CTTTATATCC AAGCAATGCA ATTCCTAGAA TCTGTGACAT CGGGAAATAC ATAGTCTCTA AAGGATAATC GGAATATTCC TGTACATAGA ACCTTCCTGA ACCTTCCTGA ACCTTCCTGA TCAATCAAAG TCAATCAAAG

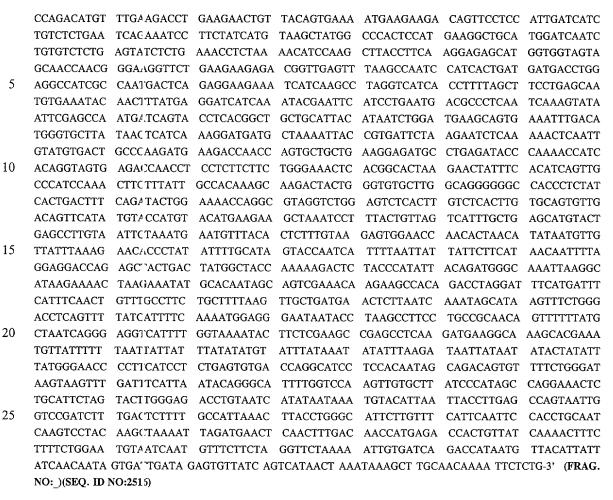






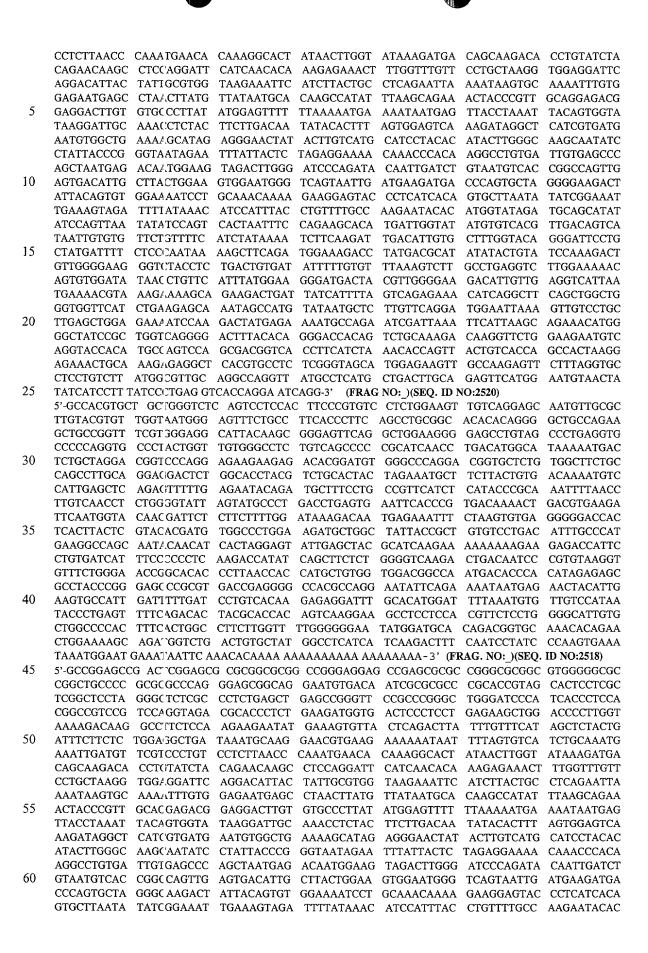


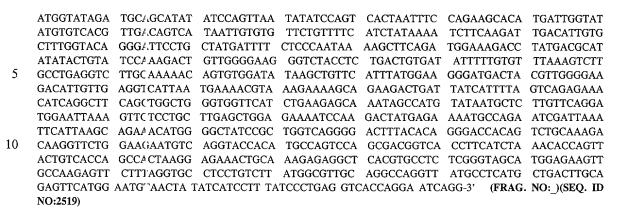




#### Human Interleukin-1 Receptor (IL-1 R) Nucleic Acids and Anti-sense Oligonucleotide Fragments

5'-GCCACGTGCT GCIGGGTCTC AGTCCTCCAC TTCCCGTGTC CTCTGGAAGT TGTCAGGAGC AATGTTGCGC TTGTACGTGT TGGTAATGGG AGTTTCTGCC TTCACCCTTC AGCCTGCGGC ACACACAGGG GCTGCCAGAA GCTGCCGGTT TCGTGGGAGG CATTACAAGC GGGAGTTCAG GCTGGAAGGG GAGCCTGTAG CCCTGAGGTG CCCCCAGGTG CCCTACTGGT TGTGGGCCTC TGTCAGCCCC CGCATCAACC TGACATGGCA TAAAAATGAC 35 TCTGCTAGGA CGGTCCCAGG AGAAGAAGAG ACACGGATGT GGGCCCAGGA CGGTGCTCTG TGGCTTCTGC CAGCCTTGCA GGAGGACTCT GGCACCTACG TCTGCACTAC TAGAAATGCT TCTTACTGTG ACAAAATGTC CATTGAGCTC AGAGTTTTTG AGAATACAGA TGCTTTCCTG CCGTTCATCT CATACCCGCA AATTTTAACC TTGTCAACCT CTGGGGTATT AGTATGCCCT GACCTGAGTG AATTCACCCG TGACAAAACT GACGTGAAGA TTCAATGGTA CAACIGATTCT CTTCTTTTGG ATAAAGACAA TGAGAAATTT CTAAGTGTGA GGGGGACCAC TCACTTACTC GTACACGATG TGGCCCTGGA AGATGCTGGC TATTACCGCT GTGTCCTGAC ATTTGCCCAT GAAGGCCAGC AAT/LCAACAT CACTAGGAGT ATTGAGCTAC GCATCAAGAA AAAAAAAGAA GAGACCATTC CTGTGATCAT TTCCCCCCTC AAGACCATAT CAGCTTCTCT GGGGTCAAGA CTGACAATCC CGTGTAAGGT GTTTCTGGGA ACCCGCACAC CCTTAACCAC CATGCTGTGG TGGACGGCCA ATGACACCCA CATAGAGAGC GCCTACCCGG GAGGCCGCGT GACCGAGGGG CCACGCCAGG AATATTCAGA AAATAATGAG AACTACATTG 45 AAGTGCCATT GATITTTGAT CCTGTCACAA GAGAGGATTT GCACATGGAT TTTAAATGTG TTGTCCATAA TACCCTGAGT TTTCAGACAC TACGCACCAC AGTCAAGGAA GCCTCCTCCA CGTTCTCCTG GGGCATTGTG CTGGCCCCAC TTTCACTGGC CTTCTTGGTT TTGGGGGGAA TATGGATGCA CAGACGGTGC AAACACAGAA CTGGAAAAGC AGA'IGGTCTG ACTGTGCTAT GGCCTCATCA TCAAGACTTT CAATCCTATC CCAAGTGAAA TAAATGGAAT GAAATAATTC AAACACAAAA AAAAAAAAA AAAAAAAA GCCGGAGCCG ACTCGGAGCG CGCGGCGCGG CCG(GAGGAG CCGAGCGCGC CGGGCGCGGC GTGGGGGCGC CGGCTGCCCC GCGCGCCCAG GGAGCGGCAG GAA'IGTGACA ATCGCGCGCC CGCACCGTAG CACTCCTCGC TCGGCTCCTA GGGCTCTCGC CCTCTGAGCT GAGC'CGGGTT CCGCCCGGGC TGGGATCCCA TCACCCTCCA CGGCCGTCCG TCCAGGTAGA CGCACCCTCT GAACIATGGTG ACTCCCTCCT GAGAAGCTGG ACCCCTTGGT AAAAGACAAG GCCTTCTCCA AGAAGAATAT GAAAGTGTTA CTCAGACTTA TTTGTTTCAT AGCTCTACTG ATTTCTTCTC TGGAGGCTGA TAAATGCAAG GAACGTGAAG AAAAAATAAT TTTAGTGTCA TCTGCAAATG AAATTGATGT TCGTCCCTGT





### 15 <u>Human Interleukin-8\* Fragments Antisense Oligonucleotide Fragments</u>

5'-GBTGTTTGTT BCCBBBGCBT CBBGBBTBGC TTTGCTBTCT BBGGBTCBCB TTTBGBCBTB GGBBBBCGCT GTBGGTCBGBB BGBTGTGCTT BCCTTCBCBC BGBGCTGCBG BBBTCBGGBBGG CTGCCBBGBBGG CCBCGGCCBGC TTGGBGTCBT GTTT3CBCBC BGTGBGGTGC TCCGGTGGCT TTTTGCTTGT GTGCTCTGCT GTCTCTG TTC CTTCCGGTGG TTTCTCCTG GCCC-3' (FRAG. NO:1834) (SEO. ID NO:1847)

- 20 5'-G CTC CGG-3' (FRAG. NO:1835) (SEQ. ID NO:1848)
  - 5'-CBBGBBTBGC-3' (FRAG. NO:1836) (SEQ. ID NO:1849)
  - 5'-CBCBC BGTGBGGT(GC-3' (FRAG. NO:1837) (SEQ. ID NO:1850)
  - 5'-BCCBBBGCBT CBBGBBTBGC-3' (FRAG. NO:1838) (SEQ. ID NO:1851)
  - 5'-GCCBBGBGBG CCBCGGCCBGC-3' (FRAG. NO:1839) (SEQ. ID NO:1852)
- 25 5'-GTG CTC CGG TGG CTT TTT-3' (FRAG. NO:1289)(SEQ. ID NO:1298)
  - 5'-GCT TGT GTG CTC TGC TGT CTC TG-3' (FRAG. NO:1290)(SEQ. ID NO:1299)
  - 5'-'TTC CTT CCG GTG GTT TCT TCC TGG CTC TTG TCC T-3' (FRAG. NO:1291)(SEQ. ID NO:1300)
  - 5'-TTC TCT TGG CCC 'ITG GCC C-3' (FRAG. NO:1292)(SEQ. ID NO:1301)
- 5'-GBTGTTTGTT BCCBBBGCBT CBBGBBTBGC TTTGCTBTCT BBGGBTCBCB TTTBGBCBTB GGBBBBCGCT GTBGGTCBGBB BGB1GTGCTT BCCTTCBCBC BGBGCTGCBG BBBTCBGGBBGG CTGCCBBGBGBG CCBCGGCCBGC TTGGBGTCBT GTTTBCBCBC BGTGBGGTGC TCCGGTGGCT TTTTGCTTGT-3' (FRAG. NO:1840) (SEQ. ID NO:1853)

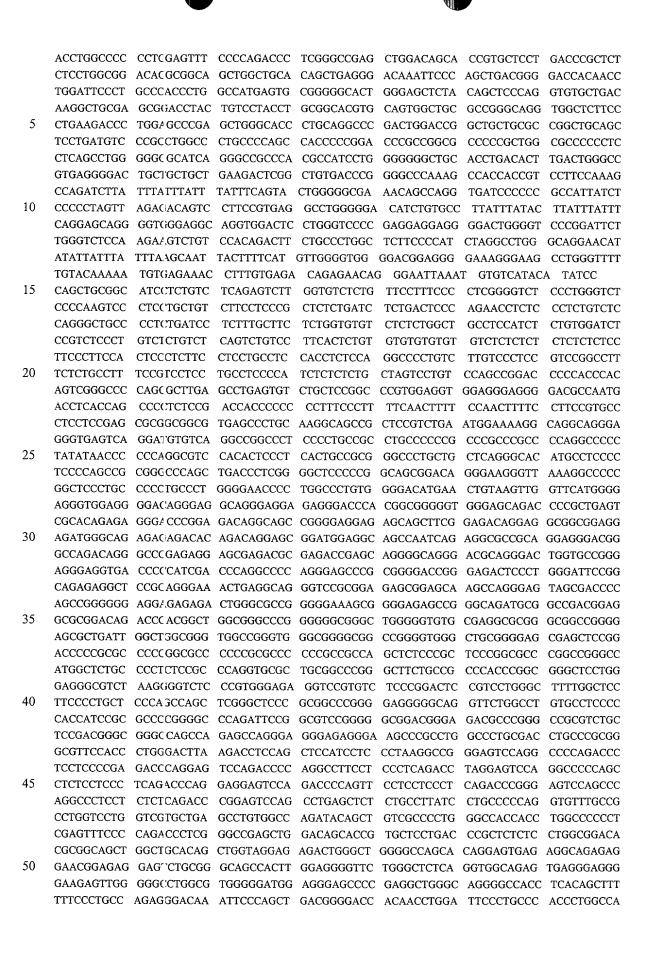
### Human IL-8 Receptor Alpha Antisense Oligonucleotide Fragments

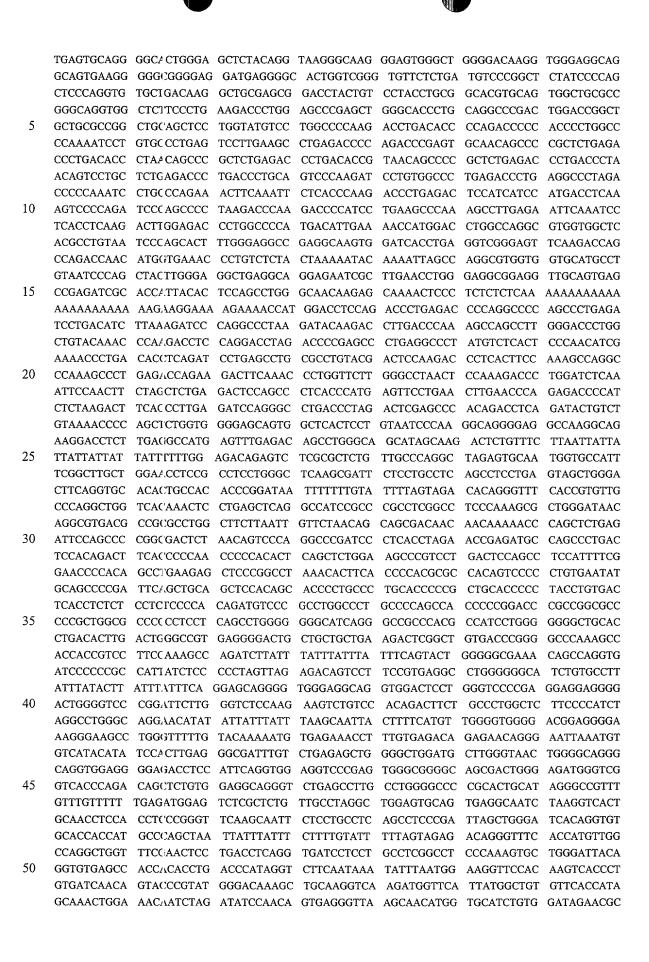
5'-ACAGGGGCTG TAATCTTCATC TGCAGGTGGC ATGCCAGTGA AATTTAGATC ATCAAAATCC CACATCTGTG GATCTGTAAT ATTIGACATG TCCTCTTCAG TTTCAGCAAT GGTTTGATCT AACTGAAGCA CCGGCCAGGB CBGGGCTGT BBTCTTCBTC TGCBGGTGGC BTGCCBGTGB BBTTTBGBTC BTCBBBBTCC CBCBTCTGTG GBTCTGTBBT BTTT3BCBTG TCCTCTTCBG TTTCBGCBB TGGTTTGBTC TBBCTGBBGC BCCGGCCBGG TGGCTCGGTG CTTCTGCCC TGTTGTTGCG GCGCTCGGTT GGTGTGCCC CTGTGGTGCT TCGTTTCCCC CTCTTTCTCT TTGTTCGGGG GTTCTTGTGG CGGGCTGCTT GTCTCGTTCC-3'(FRAG.NO:1841)(SEQ. ID NO:1854) 5'-CBGGGGC-3' (FRAG. NO:1842) (SEQ. ID NO:1855)

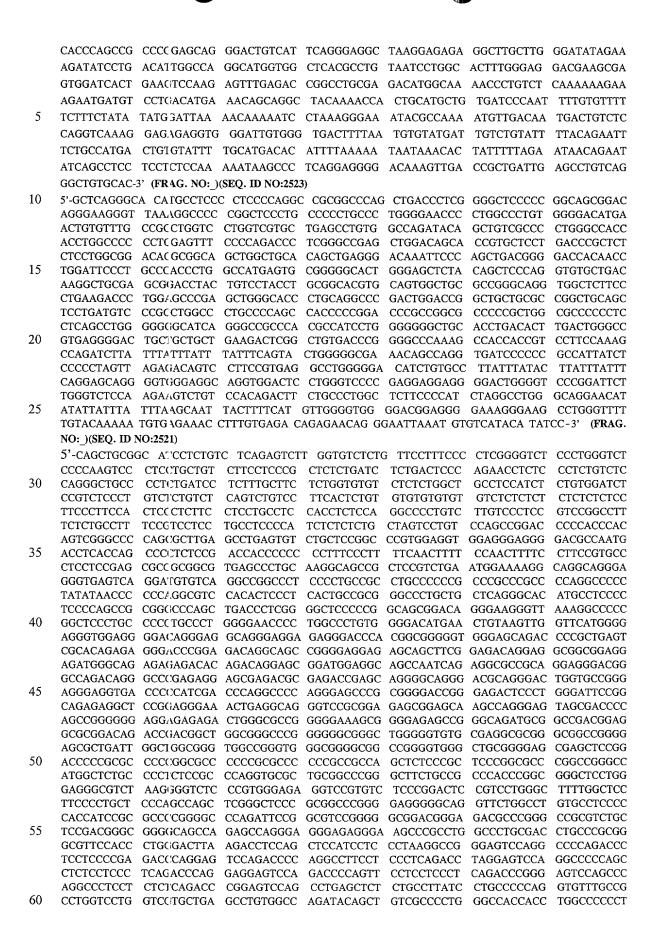
- 40 5'-GCBGGTGGC-3' (FF AG. NO:1843) (SEQ. ID NO:1856)
  - 5'-GCGGCGCTC-3' (FF AG. NO:1844) (SEQ. ID NO:1857)
  - 5'-TGGCTCGGTGCTTC'TGCCCC (FRAG. NO:1293)(SEQ. ID NO:1302)
  - 5'-TGTTGTTGCGGCGCTC (FRAG. NO:1294)(SEQ. ID NO:1303)
  - 5'-GGTTGGTGTGGCCCCTG (FRAG. NO:1295)(SEQ. ID NO:1304)
- 45 5'-TGGTGCTTCGTTTCC (FRAG, NO:1296)(SEO, ID NO:1305)
  - 5'-CCCTCTTTCTCTTTGTTC (FRAG. NO:1297)(SEQ. ID NO:1306)
  - 5'-GGGGGTTCTTGTGGC (FRAG. NO:1298)(SEQ. ID NO:1307)
  - 5'-GGGCTGCTTGTCTCGTTCC (FRAG. NO:1299)(SEQ. ID NO:1308)
- 5'-ACAGGGGCTG TAATCTTCATC TGCAGGTGGC ATGCCAGTGA AATTTAGATC ATCAAAATCC CACATCTGTG
  GATCTGTAAT ATTTGACATG TCCTCTTCAG TTTCAGCAAT GGTTTGATCT AACTGAAGCA CCGGCCAGG-3'
  (FRAG. NO:1845) (SE(). ID NO:1858)
  - 5'-B CBGGGGCTGT BBTCTTCBTC TGCBGGTGGC BTGCCBGTGB BBTTTBGBTC BTCBBBBTCC CBCBTCTGTG GBTCTGTBBT BTTTGBCBTG TCCTCTTCBG TTTCBGCBB TGGTTTGBTC TBBCTGBBGC BCCGGCCBGG-3' (FRAG. NO:1846) (SEQ. ID NO:1859)

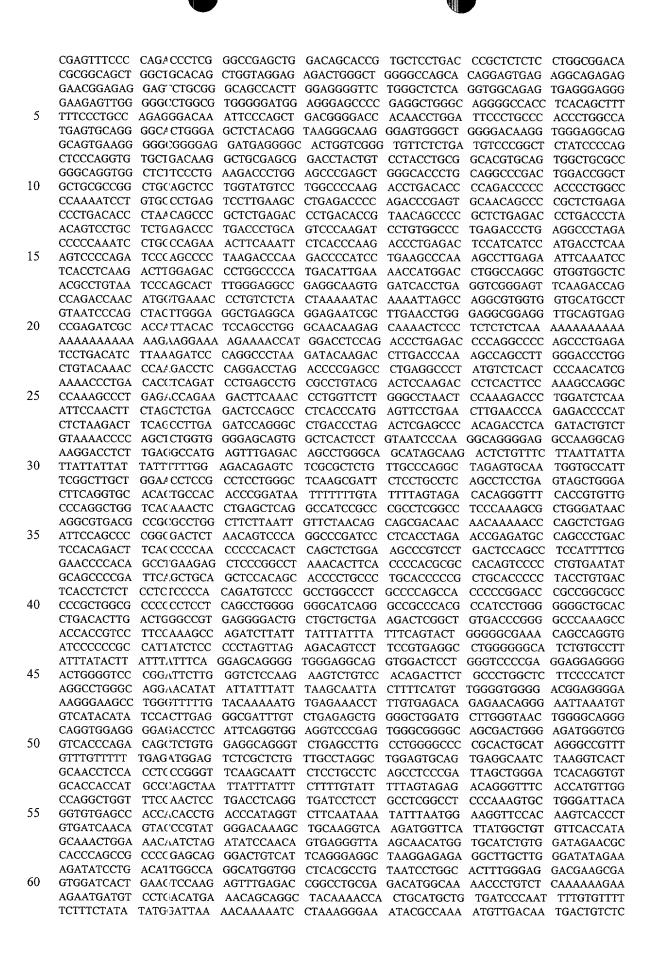
## 55 <u>Interleukin-11 (IL-11) Nucleic Acid and Antisnese Oligonucleotide Fragments</u>

5'-GCTCAGGGCA CATGCCTCCC CTCCCCAGGC CGCGGCCCAG CTGACCCTCG GGGCTCCCCC GGCAGCGGAC AGGGAAGGGT TAAAGGCCCC CGGCTCCCTG CCCCTGCCC TGGGGAACCC CTGGCCCTGT GGGGACATGA ACTGTGTTTG CCGCCTGGTC CTGGTCGTCC TGAGCCTGTG GCCAGATACA GCTGTCGCCC CTGGGCCACC









CAGGTCAAAG GAGAGAGGTG GGATTGTGGG TGACTTTTAA TGTGTATGAT TGTCTGTATT TTACAGAATT TCTGCCATGA CTGTGTATTT TGCATGACAC ATTTTAAAAA TAATAAACAC TATTTTTAGA ATAACAGAAT ATCAGCCTCC TCCTCTCCAA AAATAAGCCC TCAGGAGGGG ACAAAGTTGA CCGCTGATTG AGCCTGTCAG GGCTGTGCAC-3' (FRAG. NO: )(SEQ. ID NO:2522)

# 5 <u>Human GM-CSF Nucleic Acid and Antisense Oligonucleotide Fragments</u>

5'-CTTGBGCBGG BBGCTCTGGG GCBGGGBGCT GGCBGGGCCC BGGGGGGTGG CTTCCTGCBC TGTCCBGBGT GCBCTGTGCC BCBGCBGCBG CTGCBGGGCC BTCBGCTTCB TGGGGCTCTG GGTGGCBGGT CCBGCCBTGG GTCTGGGTGG GGCTGGGGCTG CBGGCTCCGG GCGGTCCBGCCBTGGGTCTG GGGCCTGGG CTGCBGGCTC CGGGCGGGCG GGTGCGGGCT GCGTGCTGGG GGCTGCCCCG CAGGCCCTGC GGTCCBGCCB TGGGTCTGGG

- GGCTGGGCTG CBGGCTCCGG GCGGGCGGGT GCGGGCTGCG TGCTGGGGGC TGCCCCGCAG GCCCTGC-3' (FRAG. NO:1847) (SEQ. ID NC: 1860)
  - 5'-GBGCBGG BBG-3' FRAG. NO:1848) (SEQ. ID NO: 1861)
  - 5'-GCCBCBGCBGCBGC'-3' (FRAG. NO:1849) (SEQ. ID NO: 1862)
  - 5'-GGG TGC GGG C-3' (FRAG. NO:1850) (SEQ. ID NO: 1863)
- 15 5'-GGT CCB GCC BTG 3GT CTG GG-3' (FRAG. NO:1300)(SEQ. ID NO:1309)
  - 5'-GGC TGG GCT GCB GGC TCC GG-3' (FRAG. NO:1301)(SEQ. ID NO:1310)
  - 5'-GCG GGC GGG TGC GGG CTG CGT GCT GGG-3' (FRAG. NO:1302)(SEO. ID NO:1311)
  - 5'-GGC TGC CCC GCA GGC CCT GC-3' (FRAG. NO:1303)(SEQ. ID NO:1312)
- 5'-CTTGBGCBGG BBGCTCTGGG GCBGGGBGCT GGCBGGGCCC BGGGGGGTGG CTTCCTGCBC TGTCCBGBGT

  20 GCBCTGTGCC BCBGCBGCBG CTGCBGGGCC BTCBGCTTCB TGGGGCTCTG GGTGGCBGGT CCBGCCBTGG

  GTCTGGGTGG GGCTC/GGCTG CBGGCTCCGG GC-3' (FRAG. NO:1851) (SEQ. ID NO: 1864)

## Human Tumor Necrosis Factor α Antisense Oligonucleotide Fragments

- 35 5'-GGGGCCCCCC-3' (FRAG. NO:1853) (SEQ. ID NO:1866)
  - 5'- GGG GGC CG TCT-3' (FRAG. NO:1854) (SEQ. ID NO:1867)
  - 5'-CCBGGGGBGB GBGGGGCTGG-3' (FRAG. NO:1855) (SEQ. ID NO:1868)
  - 5'-GCBCCGCCTG GBGCCCCCTGT CTTCTTGGGG BGCGCCTCCT CGGCCBGCTC CBCGTCCCGG BTCBTGCTCTT CBGTGCTCBT GGTGTCCTTT CCBGGGGBGB GBGGG-3' (FRAG. NO:1304) (SEQ. ID NO:1313)
- 45 (SEQ. ID NO:1314)
- - 5'-GCT GGT CCT CTG CTG TCC TTG CTG-3' (FRAG. NO:1655) (SEQ. ID NO:1664)
  - 5'-GTG CTC BTG GTG TCC TTT CC-3' (FRAG. NO:1656)(SEQ. ID NO:1665)
  - 5'-GCC CTG GGG CCC CCC TGT CTT CTT GGG G-3' (FRAG. NO:1657)(SEQ. ID NO:1666)
- 55 5'-CCT CTT CCC TCT (3GG GGC CG-3' (FRAG. NO:1658)(SEQ. ID NO:1667)
  - 5'-TCT CTC TCC CTC 'CT TGC GTC TCT C-3' (FRAG. NO:1659)(SEQ. ID NO:1668)
  - 5'-TCT TTC TCT CTC T'CT CTT CCC C-3' (FRAG. NO:1660)(SEQ. ID NO:1669)
  - 5'-TTT CCC GCT CTT 'CT GTC TC-3' (FRAG. NO:1661)(SEQ. ID NO:1670)
  - 5'-GGT GTC TGG TTT 'TCT CTC TCC-3' (FRAG. NO:1662)(SEQ. ID NO:1671)

5'-GCT GGC TGC CTG TCT GGC CTG CGC TCT T-3' (FRAG. NO:1663)(SEQ. ID NO:1672)
5'-GGC CTG TGC TGT ICC TCC-3' (FRAG. NO:1664)(SEQ. ID NO:1673)
5'-TCC GGT TCC TGT ICCT CTC TGT CTG TC-3' (FRAG. NO:1665)(SEQ. ID NO:1674)
5'-GCC CCC TCT GGG GTC TCC CTC TGG C-3' (FRAG. NO:1666)(SEQ. ID NO:1675)
5'-GTG GTG GTC TTG ITG CTT-3' (FRAG. NO:1667)(SEQ. ID NO:1676)
5'-GGG CTG GGC TCC GTG TCT C-3' (FRAG. NO:1668)(SEQ. ID NO:1677)
5'-CBG TGC TCB TGG IGT CC-3' (FRAG. NO:1669)(SEQ. ID NO:1678)

5'-GCT GBG GGB GCG TCT GCT GGC-3' (FRAG. NO:1670)(SEQ. ID NO:1679)

### Human Leukotriene C4 Synthase Nucleic Acids and Antisense Oligonucleotide Fragments

- 5'-CTCGGTBGBC GCCCTCGBBC TCGGGTGGGC CGGTGGTGBG CGGCGGCBCB CGCGGBBGGC CCTGCGCGCC GBGBTCBCCTG CBGGGBGBG TBGGCTTGCB GCBGGBCTCC CBGGBGGGTG BCBGCBGCCB GTBGBGCTBC CTCGTCCTTC BTGGTBCCGT CGGTGTGGTG GCBCGGGCTG TGTGTGBBGG CGBGCTGGC CCCGTCTGCT GCTCCTCGTG CCGCCTCGTC CTTCA TGG TA CCGTCGGTGT GGTGGCCTCG GGTGGGCCGG TGGTGGGGCCG CGCGCGCTCG CGTCGCTCCT CCCCGGCTCCT CGGCCCGGGG GCCTTGGTCT CCCTCGTCCT
- 15 TCBTGGTBCC G-3' (FRAG. NO:1856) (SEQ ID NO: 1869)
  5'-GCB GCBGGBC-3' (FRAG. NO:1857) (SEQ ID NO: 1870)
  5'-CCCGGCTCCG-3' (FRAG. NO:1858) (SEQ ID NO: 1871)
  5'-CGGCCCGGGG GCC-3' (FRAG. NO:1859) (SEQ ID NO:1872)
  5'-CB CGCGG-3' (FRAG. NO:1860) (SEQ ID NO: 1873)
- 5'-GCC CCG TCT GCT GCT CCT CGT GCC G-3' (FRAG. NO:1307)(SEQ. ID NO:1316)
  5'-CCT CGT CCT TCA 'FGG TAC CGT CGG TGT GGT GGC-3' (FRAG. NO:1308)(SEQ. ID NO:1317)
  5'-CTC GGG TGG GCC GGT GGT G-3' (FRAG. NO:1309)(SEQ. ID NO:1318)
  5'-GGG CGC GCG CGC TCG CGT-3' (FRAG. NO:1310)(SEQ. ID NO:1319)
- 5'-GGC TCC GGC TCT TCT TTC CCG GCT CCG TCG GCC CGG GGG CCT TGG TCT C-3'(FRAG.NO:1311)(SEQ.ID NO:1320)
  5'-CCT CGT CCT TCB IGG TBC CG-3' (FRAG. NO:1312)(SEQ. ID NO:1321)
  5'-CTCGGTBGBC GCGCTCGBBC TCGGGTGGGC CGGTGGTGBG CGGCGGCGBCB CGCGGBBGGC CCTGCGCCC GBGBTCBCCTG CBGGGBGBG TBGGCTTGCB GCBGGBCTCC CBGGBGGGTG BCBGCBGCCB GTBGBGCTBC CTCGTCCTTC BTGGT'BCCGT CGGTGTGGTG GCBCGGGCTG TGTGTGBBGG CGBGCTGG-3' (FRAG.NO:1861)
  (SEQ ID NO:1874)

# 30 <u>Human Endothel n-1 Nucleic Acids and Antisense Oligonucleotide Fragments</u>

5'-BCCGGCGGBG CC3CCBGGGT GGBCTGGGBG TGGGTTTCTC CCCGCCGTTC TCBCCCBCCG CGCTGBGCTC
BGCGCCTBBG BCTGCTGTTT CTGGBGCTCC TTGGCBBGCC BCBBBCBGCB GBGBGBBBBT CBTGBGCBBB
TBBTCCBTTC TGBBBBBBBG GGBTCBBBBB CCTCCCGTTC CCCGTTCGCC TGGCGCGCG TGCGGGTTCC
TCGTGGGTTT CTCCCCGCCG TTCTCCGGTC TGTTGCCTTT GTGGTCTTTT TCCTGCTTGG CGTCTTTTCC TTTCTTTTGTG CTCGGTTGTG GGTCCCCTGG TCCTTTGCCC TGTGTGTTTC
TCTTGTGGG CTTCTTGTCT TTTTGGCTGT GTTCCTCGTG GGTTTCTCC CGCCGTTCT CGGTCTTG
CCTTTGTGGG CTTCTTGTCT TTTTGGCTGT TCTTTTCCTG CTTGGCGTCT TTTCCTTTCT TTGTGTCTGGG
TTGTGGGTCC GCTGC TCCTT TGCCCTGTG GTTTCTGCTG-3' (FRAG. NO:1862) (SEQ. ID NO:1875)
5'-CCGGCGGBG CCGCCBGGGT GGBC-3' (FRAG. NO:1863) (SEQ. ID NO:1876)

- 40 5'-CCGCCBGGG-3' (FRAG. NO:1864) (SEQ. ID NO:1877)
  5'-GGCGCGCGC-3' (FRAG. NO:1865) (SEQ. ID NO:1878)
  5'-GTGGGTCCGC-3' (FRAG. NO:1866) (SEQ. ID NO:1879)
  5'-CCCGTTCGCCTGGCGC-3' (FRAG. NO:1313)(SEQ. ID NO:1322)
  5'-GCGCTGCGGGTTCCTC-3' (FRAG. NO:1314)(SEQ. ID NO:1323)
- 5'-GTGGGTTTCTCCC('GCCGTTCTC-3' (FRAG. NO:1315)(SEQ. ID NO:1324)
  5'-CGGTCTGTTGCCT'TGTGGG -3' (FRAG. NO:1316)(SEQ. ID NO:1325)
  5'-CTTCTTGTCTTTTT 3GCT-3' (FRAG. NO:1317)(SEQ. ID NO:1326)
  5'-GTTCTTTCCTGCTTGGC-3' (FRAG. NO:1318)(SEQ. ID NO:1327)
  5'-GTCTTTTCCTTCTT-3' (FRAG. NO:1319)(SEQ. ID NO:1328)
- 50 5'-TGTGCTCGGTTGTGGGTC-3' (FRAG. NO:1320)(SEQ. ID NO:1329)
  5'-CGCTGGTCCTTTGCC-3' (FRAG. NO:1321)(SEQ. ID NO:1330)
  5'-CTGTGTGTTTCTGCTG-3' (FRAG. NO:1322)(SEQ. ID NO:1331)
  5'-CCCGTTCGCCTGGCGC-3' (FRAG. NO:1323)(SEQ. ID NO:1332)
  5'-GCGCTGCGGGTTCCTC-3' (FRAG. NO:1324)(SEQ. ID NO:1333)
- 55 5'-GTGGGTTTCTCCCCGCCGTTCTC-3' (FRAG. NO:1325(SEQ. ID NO:1334)
  5'-CGGTCTGTTGCCTTTGTGGG-3' (FRAG. NO:1326)(SEQ. ID NO:1335)
  5'-CTTCTTGTCTTTTTGGCT-3' (FRAG. NO:1327)(SEQ. ID NO:1336)
  5'-GTTCTTTTCCTGCTTGGC-3' (FRAG. NO:1328)(SEQ. ID NO:1337)
  5'-GTCTTTTCCTTTCTT-3' (FRAG. NO:1329)(SEQ. ID NO:1338)
- 60 5'-TGTGCTCGGTTGT(\(\)GGTC-3'\) (FRAG. NO:1330)(SEQ. ID NO:1339)

5'-CGCTGGTCCTTTGC C-3' (FRAG. NO:1331)(SEQ. ID NO:1340) 5'-CTGTGTGTTTCTGCTG-3' (FRAG. NO:1332)(SEO. ID NO:1341)

#### Endothelin Receptor ET-B Nucleic Acids and Antisense Oligonucleotide Fragments

- 5'-GCCCTGTCGG GC'3GGAAGCC TCTCTCCTCT CCCCAGATC CGCGACAGGC CGCAGGCAAG AACCAGCGCA
  ACCAGGGCGC GTCC'GCACAG ACTTGGAGGC GGCTGCATGC TGCTACCTGC TCCAGAAGCG TCCGGTGGCC
  GCCGCGCC CTGTC'3GGCG GGBBGCCTCT CTCCTCTCCC CBGBTCCGCG BCBGGCCGCB GGCBBGBBCC
  BGCGCBBCCB GGGCGCGTCC GCBCBGBCTT GGBGGCGGCT GCBTGCTGCT BCCTGCTCGGGCG GGBBGCCTCCG
  GTGGCCGCCG CGCGTCCGGT GGCCGCCGCG CCTCTCTCCT CTCCCCGTGG CCCTGTCGGG CGGGTCCTGC
  CGTCCTGTCT CCTTT'TCTTT TGCTGTCTTG TCTTCCCGTC TCTGCTTT-3' (FRAG. NO: 1867) (SEO. ID NO: 1880)
- 10 5'-CGGGCG GGBBGCC-3' (FRAG. NO: 1868) (SEQ. ID NO: 1881) 5'-CGGGCGGG-3' (FRAG. NO: 1869) (SEQ. ID NO: 1882) 5'-CCGCBCBGBC-3' (FRAG. NO: 1870) (SEQ. ID NO: 1883) 5'-GCGTCCGGTGGCCGCCGC-3' (FRAG. NO:1333)(SEQ. ID NO:1342) 5'-GCCTCTCTCCTCCCC-3' (FRAG. NO:1334)(SEQ. ID NO:1343)
- 5'-GTGGCCCTGTCGGGCGGG-3' (FRAG. NO:1335)(SEQ. ID NO:1344) 5'-TCCTGCCGTCCTGTCTCCTTT-3' (FRAG. NO:1336)(SEQ. ID NO:1345) 5'-TCTTTTGCTGTCTT 3T-3' (FRAG. NO:1337)(SEQ. ID NO:1346)

5'-CTTCCCGTCTCTGCTTT-3' (FRAG. NO:1338)(SEQ. ID NO:1347)

- 5'-GCCCTGTCGG GC3GGAAGCC TCTCTCCTCT CCCCAGATC CGCGACAGGC CGCAGGCAAG AACCAGCGCA
  ACCAGGGCGC GTCCGCACAG ACTTGGAGGC GGCTGCATGC TGCTACCTGC TCCAGAAGCG TCCGGTGGCC
  GCCGC-3' (FRAG. NO: 1871) (SEQ. ID NO: 1884)
- 5'-GCCCTGTCGG GCGGGBBGCC TCTCTCCTCT CCCCBGBTCC GCGBCBGGCC GCBGGCBBGB BCCBGCGCB BCCBGGGCG GTCCCCCBCBG BCTTGGBGGC GGCTGCBTGC TGCTBCCTGC TCCBGBBGCG TCCGGTGGCC GCCGC-3' (FRAG. NO: 1872) (SEQ. ID NO: 1885)

# 25 Endothelin ETA Receptor Nucleic Acids and Antisense Oligonucleotide Fragments

TTGBGGCBBB TTTGBGGB-3' (FRAG. NO:1873) (SEQ. ID NO: 1886)

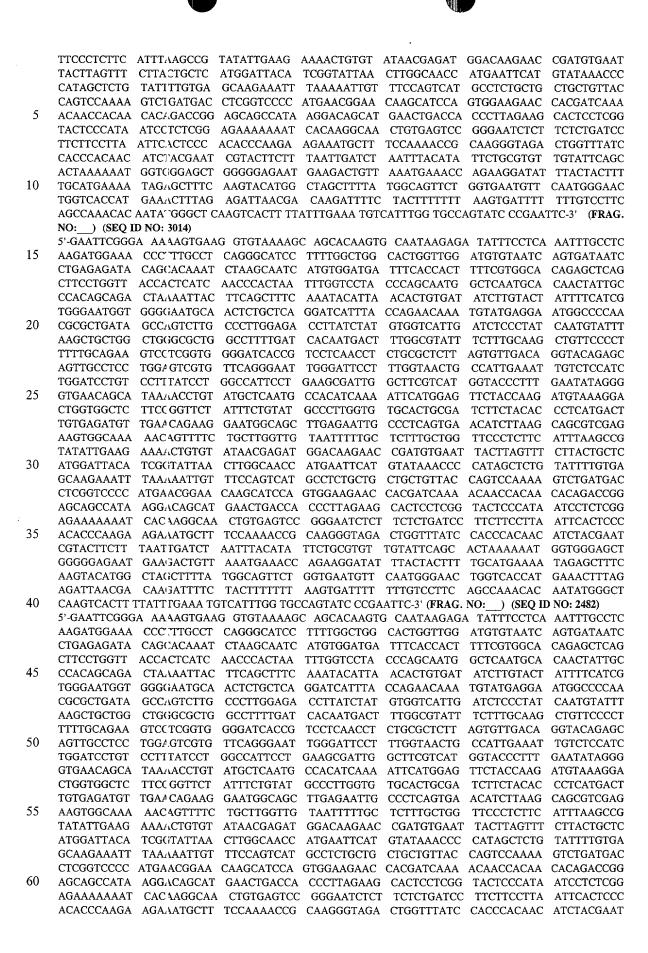
5'-GBGGCBBBGGG-3' (FRAG. NO:1874) (SEQ. ID NO: 1887)

5'-GCCBGCCBB BBGG 3-3' (FRAG. NO:1875) (SEQ. ID NO: 1888)

- 40 5'-CGCCTGGGCC C-3' (FRAG. NO:1876) (SEQ. ID NO: 1889)
  - 5'-GTCTGTCCTCCCCC'TCTCCTCCC-3' (FRAG. NO:1339)(SEQ. ID NO:1348)
  - 5'-ACTGCTTCTCCCGCGGG-3' (FRAG. NO:1340)(SEQ. ID NO:1349)
  - 5'-GCTTCCCCGGCTT('-3' (FRAG. NO:1341)(SEQ. ID NO:1350)
  - 5'-GGGTGGCCGGTGTCCCGGGCTCCGGCGCGCGCGCG' (FRAG. NO:1342)(SEQ. ID NO:1351)
- 45 5'-GGCTTCGGCTGC-3 (FRAG. NO:1343)(SEO. ID NO:1352)
  - 5'-GGGTGGGTGGCGC3G-3' (FRAG. NO:1344)(SEQ. ID NO:1353)
  - 5'-GCTGCCGGGTCCGCGCGCGCCCTGGGCC-3' (FRAG. NO:1345)(SEQ. ID NO:1354)
  - 5'-CTTGTGCTGCTTTT-3' (FRAG. NO:1346(SEQ. ID NO:1355)
  - 5'-TGCTTGTTCCGTTC-3' (FRAG. NO:1347)(SEQ. ID NO:1356)
- 50 5'-TGGCTGCTCCGGTCTGTTGTTGTGGTTGTTTTG-3' (FRAG. NO:1348)(SEQ. ID NO:1357)
  - 5'-TTTCTTCTTGGGTGTGGG-3' (FRAG. NO:1349)(SEQ. ID NO:1358)
  - 5'-CCTTGCGGTTTTGC-3' (FRAG. NO:1350)(SEQ. ID NO:1359)
  - 5'-CTGTGGGCCCTTT(i-3' (FRAG. NO:1351)(SEQ. ID NO:1360)
  - 5'-GGGCCTTGGCTTCl'GGCTC-3' (FRAG. NO:1352)(SEQ. ID NO:1361)
- 55 5'-CATCCACATG ATIGCTTAGA TTTGTGCTGT ATCTCTCAGG ATTATCACTG ATTACACATC CAACCAGTGC CAGCCAAAAG GATCCCCTGA GGCAAAGGGT TTCCATCTTG AGGCAAATTT GAGGA-3' (FRAG.NO:1353) (SEQ.ID NO:1362)
  - 5'-CBTCCBCBTG BT'IGCTTBGB TTTGTGCTGT BTCTCTCBGG BTTBTCBCTG BTTBCBCBTC CBBCCBGTGC CBGCCBBBBG GBTGCCCTGB GGCBBBGGGT TTCCBTCTTG BGGCBBBTTT GBGGB-3' (FRAG. NO:1354)(SEQ. ID NO:1363)

## Endothelin Receptor A Nucleic Acid and Antisense Oligonucleotide Fragments

5'-GCCACCATGG AAACCCTTTG CCTCAGGGCA TCCTTTTGGC TGGCACTGGT TGGATGTGTA ATCAGTGATA ATCCTGAGAG ATACAGCACA AATCTAAGCA ATCATGTGGA TGATTTCACC ACTTTTCGTG GCACAGAGCT CAGCTTCCTG GTTACCACTC ATCAACCCAC TAATTTGGTC CTACCCAGCA ATGGCTCAAT GCACAACTAT TGCCCACAGC AGACTAAAAT TACTTCAGCT TTCAAATACA TTAACACTGT GATATCTTGT ACTATTTTCA TCGTGGGAAT GGTCIGGGAAT GCAACTCTGC TCAGGATCAT TTACCAGAAC AAATGTATGA GGAATGGCCC CAACGCGCTG ATAGCCAGTC TTGCCCTTGG AGACCTTATC TATGTGGTCA TTGATCTCCC TATCAATGTA TGGCTGGGCG CTGGCCTTTT GATCACAATG ACTTTGGCGT ATTTCTTTGC AAGCTGTTCC CCTTTTTGCA GAAGTCCTCG GTGGGGATCA CCGTCCTCAA CCTCTGCGCT CTTAGTGTTG ACAGGTACAG AGCAGTTGCC TCCTGGAGTC GTGTTCAGGG AATTGGGATT CCTTTGGTAA CTGCCATTGA AATTGCCTCC ATCTGGATCC TGTCCTTTAT CCTGGCCATT CCTGAAGCGA TTGGCTTCGT CATGGTACCC TTTGAATATA GGGGTGGACA GCATAAAACC TGTATGCTCA ATGCCACATC AAAATTCATG GAGTTCTACC AAGATGTAAA GGACTGGTGG CTCTTCGGGT TCTATTTCTG TATGCCCTTG GTGTGCACTG CGATCTTCTA CACCCTCATG ACTGGTGAGA TGTTGAACAG AAGGAATGGC AGCTTGAGAA TTGCCCTCAG TGAACATCTT AAGCAGCGTC GAGAAGTGGC AAAAACAGTT TTC GCTTGG TTGTAATTTT TGCTCTTTGC TGGTTCCCTC TTCATTTAAG CCGTATATTG AAGAAAACTG TGTATAACGA GATGGACAAG AACCGATGTG AATTACTTAG TTTCTTACTG CTCATGGATT ACATCGGTAT TAACTTGGCA ACCATGAATT CATGTATAAA CCCCATAGCT CTGTATTTTG TGAGCAAGAA ATTTAAAAAT TGTTTCCAGT CATGCCTCTG CTGCTGCTGT TACCAGTCCA AAAGTCTGAT GACCTCGGTC CCCATGAACG GAACAAGCAT CCAGTGGAAG AACCACGATC AAAACAACCA CAACACAGAC CGGAGCAGCC 20 ATAAGGACAG CATGAACTGA CCACCCTTAG AAGCACTCCT GAATTCGGGA AAAAGTGAAG GTGTAAAAGC AGCACAAGTG CAA'AAGAGA TATTTCCTCA AATTTGCCTC AAGATGGAAA CCCTTTGCCT CAGGGCATCC TTTTGGCTGG CACTGGTTGG ATGTGTAATC AGTGATAATC CTGAGAGATA CAGCACAAAT CTAAGCAATC ATGTGGATGA TTTC/ACCACT TTTCGTGGCA CAGAGCTCAG CTTCCTGGTT ACCACTCATC AACCCACTAA TTTGGTCCTA CCCAGCAATG GCTCAATGCA CAACTATTGC CCACAGCAGA CTAAAATTAC TTCAGCTTTC AAATACATTA ACACTGTGAT ATCTTGTACT ATTTTCATCG TGGGAATGGT GGGGAATGCA ACTCTGCTCA GGATCATTTA CCACAACAA TGTATGAGGA ATGGCCCCAA CGCGCTGATA GCCAGTCTTG CCCTTGGAGA CCTTATCTAT GTGCTCATTG ATCTCCCTAT CAATGTATTT AAGCTGCTGG CTGGGCGCTG GCCTTTTGAT CACAATGACT TTGGCGTATT TCTTTGCAAG CTGTTCCCCT TTTTGCAGAA GTCCTCGGTG GGGATCACCG TCCTCAACCT CTGCGCTCTT AGTGTTGACA GGTACAGAGC AGTTGCCTCC TGGAGTCGTG TTCAGGGAAT TGGGATTCCT TTGCTAACTG CCATTGAAAT TGTCTCCATC TGGATCCTGT CCTTTATCCT GGCCATTCCT GAAGCGATTG GCTTCGTCAT GGTACCCTTT GAATATAGGG GTGAACAGCA TAAAACCTGT ATGCTCAATG CCACATCAAA ATTCATGGAG TTCTACCAAG ATGTAAAGGA CTGGTGGCTC TTCGGGTTCT ATTTCTGTAT GCCCTTGGTG TGCACTGCGA TCTTCTACAC CCTCATGACT TGTGAGATGT TGAACAGAAG GAATGGCAGC TTGAGAATTG CCCTCAGTGA ACATCTTAAG CAGCGTCGAG AAGTGGCAAA AACAGTTTTC TGCTTGGTTG TAATTTTTGC TCTTIGCTGG TTCCCTCTTC ATTTAAGCCG TATATTGAAG AAAACTGTGT ATAACGAGAT GGACAAGAAC CGAIGTGAAT TACTTAGTTT CTTACTGCTC ATGGATTACA TCGGTATTAA CTTGGCAACC ATGAATTCAT GTATAAACCC CATAGCTCTG TATTTTGTGA GCAAGAAATT TAAAAATTGT TTCCAGTCAT GCCTCTGCTG CTGCTGTTAC CAGTCCAAAA GTCTGATGAC CTCGGTCCCC ATGAACGGAA CAAGCATCCA GTGGAAGAAC CACGATCAAA ACAACCACAA CACAGACCGG AGCAGCCATA AGGACAGCAT GAACTGACCA 40 CCCTTAGAAG CACTCCTCGG TACTCCCATA ATCCTCTCGG AGAAAAAAT CACAAGGCAA CTGTGAGTCC GGGAATCTCT TCTCTGATCC TTCTTCCTTA ATTCACTCCC ACACCCAAGA AGAAATGCTT TCCAAAACCG CAAGGGTAGA CTGGTTTATC CACCCACAAC ATCTACGAAT CGTACTTCTT TAATTGATCT AATTTACATA TTCTGCGTGT TGTATCAGC ACTAAAAAT GGTGGGAGCT GGGGGAGAAT GAAGACTGTT AAATGAAACC AGAAGGATAT TTACTACTTT TGCATGAAAA TAGAGCTTTC AAGTACATGG CTAGCTTTTA TGGCAGTTCT GGTGAATGTT CAATGGGAAC TGGTCACCAT GAAACTTTAG AGATTAACGA CAAGATTTTC TACTTTTTTT AAGTGATTTT TTTGTCCTTC AGCCAAACAC AATATGGGCT CAAGTCACTT TTATTTGAAA TGTCATTTGG 45 TGCCAGTATC CCGAATTC GAATTCGGGA AAAAGTGAAG GTGTAAAAGC AGCACAAGTG CAATAAGAGA TATTTCCTCA AATTTGCCTC AAGATGGAAA CCCTTTGCCT CAGGGCATCC TTTTGGCTGG CACTGGTTGG ATGTGTAATC AGTCATAATC CTGAGAGATA CAGCACAAAT CTAAGCAATC ATGTGGATGA TTTCACCACT TTTCGTGGCA CAGAGCTCAG CTTCCTGGTT ACCACTCATC AACCCACTAA TTTGGTCCTA CCCAGCAATG
GCTCAATGCA CAACTATTGC CCACAGCAGA CTAAAATTAC TTCAGCTTTC AAATACATTA ACACTGTGAT ATCTTGTACT ATTTICATCG TGGGAATGGT GGGGAATGCA ACTCTGCTCA GGATCATTTA CCAGAACAAA TGTATGAGGA ATGGCCCCAA CGCGCTGATA GCCAGTCTTG CCCTTGGAGA CCTTATCTAT GTGGTCATTG ATCTCCCTAT CAAIGTATTT AAGCTGCTGG CTGGGCGCTG GCCTTTTGAT CACAATGACT TTGGCGTATT TCTTTGCAAG CTG1TCCCCT TTTTGCAGAA GTCCTCGGTG GGGATCACCG TCCTCAACCT CTGCGCTCTT AGTGTTGACA GGTACAGAGC AGTTGCCTCC TGGAGTCGTG TTCAGGGAAT TGGGATTCCT TTGGTAACTG CCATTGAAAT TGTCTCCATC TGGATCCTGT CCTTTATCCT GGCCATTCCT GAAGCGATTG GCTTCGTCAT GGTACCCTTT GAATATAGGG GTGAACAGCA TAAAACCTGT ATGCTCAATG CCACATCAAA ATTCATGGAG TTCTACCAAG ATGT'AAAGGA CTGGTGGCTC TTCGGGTTCT ATTTCTGTAT GCCCTTGGTG TGCACTGCGA TCTTCTACAC CCTCATGACT TGTGAGATGT TGAACAGAAG GAATGGCAGC TTGAGAATTG CCCTCAGTGA ACATCTTAAG CAGCGTCGAG AAGTGGCAAA AACAGTTTTC TGCTTGGTTG TAATTTTTGC TCTTTGCTGG



CGTACTTCTT TAATTGATCT AATTTACATA TTCTGCGTGT TGTATTCAGC ACTAAAAAAT GGTGGGAGCT GGGGGAGAAT GAAGACTGTT AAATGAAACC AGAAGGATAT TTACTACTTT TGCATGAAAA TAGAGCTTTC AAGTACATGG CTAGCTTTTA TGGCAGTTCT GGTGAATGTT CAATGGGAAC TGGTCACCAT GAAACTTTAG AGATTAACGA CAA'GATTTTC TACTTTTTTT AAGTGATTTT TTTGTCCTTC AGCCAAACAC AATATGGGCT CAAGTCACTT TTATTIGAAA TGTCATTTGG TGCCAGTATC CCGAATTC-3'(FRAG. NO: \_\_) (SEQ ID NO: 2470) 5'-GCCACCATGG AAACCCTTTG CCTCAGGGCA TCCTTTTGGC TGGCACTGGT TGGATGTGTA ATCAGTGATA ATCCTGAGAG ATACAGCACA AATCTAAGCA ATCATGTGGA TGATTTCACC ACTTTTCGTG GCACAGAGCT TCCTGGAGTC GTGTTCAGGG AATTGGGATT CCTTTGGTAA CTGCCATTGA AATTGCCTCC ATCTGGATCC TGTCCTTTAT CCTGGCCATT CCTGAAGCGA TTGGCTTCGT CATGGTACCC TTTGAATATA GGGGTGGACA GCATAAAACC TGTATGCTCA ATGCCACATC AAAATTCATG GAGTTCTACC AAGATGTAAA GGACTGGTGG CTCTTCGGGT TCTATTTCTG TATGCCCTTG GTGTGCACTG CGATCTTCTA CACCCTCATG ACTGGTGAGA TGTTGAACAG AAGGAATGGC AGCTTGAGAA TTGCCCTCAG TGAACATCTT AAGCAGCGTC GAGAAGTGGC AAAAACAGTT TTC GCTTGG TTGTAATTTT TGCTCTTTGC TGGTTCCCTC TTCATTTAAG CCGTATATTG AAGAAAACTG TGTATAACGA GATGGACAAG AACCGATGTG AATTACTTAG TTTCTTACTG CTCATGGATT ACATCGGTAT TAACTTGGCA ACCATGAATT CATGTATAAA CCCCATAGCT CTGTATTTTG TGAGCAAGAA ATTTAAAAAT TGTTTCCAGT CATGCCTCTG CTGCTGCTGT TACCAGTCCA AAAGTCTGAT GACCTCGGTC CCCATGAACG GAACAAGCAT CCAGTGGAAG AACCACGATC AAAACAACCA CAACACAGAC CGGAGCAGCC ATAAGGACAG CATGAACTGA CCACCCTTAG AAGCACTCCT-3' (FRAG. NO: ) (SEQ ID NO: 2469)

## Substance P Antisense Nucleic Acids and Oligonucleotide Antisense Oligonucleotide Fragments

5'-CTGCTGBGGC TT'3GGTCTCC GGGCGBTTCT CTGCBGBBGB TGCTCBBBGG GCTCCGGCBG TTCCTCCTTG BTCTGGTCGCT GTCGTBCCBG TCGGBCCBGT BBTTCBGBTC BTCBTTGGCT CCTBTTTCTT CTGCBBBCBG CTGBGTGGBG BCBI:GBBBBB BGBCTGCCBB GGCCBCGBGG BTTTTCBTGT TGGBTTTTGC GBCGGBCBGT CCCGCGGGGT GCTGAGTTTC TCTGGTTCCT CCGBGCGCBC GTGGTCGCTC CGCGTTTCTC TGGTTCCTCC 

NO:1877) (SEQ ID NO: 1890)

5'-CTCC GGGCGB-3' (FRAG. NO:1878) (SEQ ID NO: 1891)

5'-GGCCBCGBGG-3' (FRAG. NO:1879) (SEQ ID NO: 1892)

5'-GGGTCTCCGGGCG 3' (FRAG. NO:1880) (SEQ ID NO: 1893)

- 5'-GGG TCTCCGGGCG G-3' (FRAG. NO:1881) (SEQ ID NO:1894)
  - 5'-CGTGGTCGCTCCGC-3' (FRAG. NO:1355)(SEQ. ID NO:1364)
  - 5'-GTTTCTCTGGTTCCTCCG-3' (FRAG. NO:1356)(SEQ. ID NO:1365)
  - 5'-GTCCCGCGGGGTGCTG-3' (FRAG. NO:1357)(SEQ. ID NO:1366)
  - 5'-TCTGGTCGCTGTC('T-3' (FRAG. NO:1358)(SEQ. ID NO:1367)
- 5'-GGCTTGGGTCTCC(jGGCG-3' (FRAG. NO:1359)(SEQ. ID NO:1368) 5'-GTTTCCTTCCTTTTCCGC-3' (FRAG. NO:1360)(SEQ. ID NO:1369)

  - 5'-CTGCTGBGGC TT'GGGTCTCC GGGCGBTTCT CTGCBGBBGB TGCTCBBBGG GCTCCGGCBG TTCCTCCTTG BTCTGGTCGCT GTCGTBCCBG TCGGBCCBGT BBTTCBGBTC BTCBTTTGGCT CCTBTTTCTT CTGCBBBCBG CTGBGTGGBG BCBI/GBBBBB BGBCTGCCBB GGCCBCGBGG BTTTTCBTGT TGGBTTTTGC **GBCGGBCBGT** CCCGCGGGGT GCTGAGTTTC TCTGGTTCCT CCGBGCGCB-3' (FRAG. NO:1882) (SEQ ID NO: 1895)

## Substance P Receptor Nucleic Acids and Antisense Oligonucleotide Fragments

5'-GGGCTBBGBT GBTCCBCBTC BCTBCCBCGT TGCCCBCCBC BGBGGTCBCC BCBBTGBCCG TGTBGGCBGC TGCCCBBBGG BCBETTTGCC BGGCTGGTTG CBCGBBCTGB TTGGGTTCCG BGGTGTTBGT GGBGBTGTTT GGGGBGBGGT CTG3GTCCBC CGGGBGGBCG TTBTCCBTTT CGBBGCTBGG CGGTBBBGCC CTBCTBTCTG
TBCBCBBCCC CCCTCTGCBG CBGBGTCCTG TCGTGGCGCC TGGGGCTCBG GGTCCGGGC TAAGATGATC CACATCACTA CCACGTTGCC CACCACAGAG GTCACCACAA TGACCGTGTA GGCAGCTGCC CAAAGGACAA TTTGCCAGGC TGG1TGCACG AACTGATTGG GTTCCGAGGT GTTAGTGGAG ATGTTTGGGG AGAGGTCTGA GTCCACCGGG AGGACGTTAT CCATTTCGAA GCTAGGCGGT AAAGCCCTAC TATCTGTACA CAACCCCCCT CTGCAGCAGA GTCCTGTCGT GGCGCCTGGG GCTCAGGGTC CGTCCTGTCG TGGCGCCTGG GGCTCTTCTT 55 TTGTGGGCTC TTTCGTGGCT GTGGCTGTGG TCTCTGTGGT TGCTGCCCTG GGTCTGGGGG TGTGGCCTTG

GGGCCGTCCT CTGGCTCCTC CTCGTGGGCC CCC-3' (FRAG. NO:1883) (SEQ. ID NO:1896)

- 5'-GGGBGGBCG-3' (FRAG. NO:1884) (SEQ. ID NO:1897)
- 5'-GGGTC CG-3' (FRAG. NO:1885) (SEQ. ID NO:1898)
- 5-'GGGCC CCC-3' (FRAG. NO:1886) (SEQ. ID NO:1899)
- 5'-GTCCTGTCGTGGCGCCTGGGGCTC-3' (FRAG. NO:1361)(SEQ. ID NO:1370)

- 5'-TTCTTTTGTGGGCT-3' (FRAG. NO:1362)(SEQ. ID NO:1371)
- 5'-CTTTGGTGGCTGT(GCTG-3' (FRAG. NO:1363)(SEQ. ID NO:1372)
- 5'-TGGTCTCTGTGGTTG-3' (FRAG. NO:1364)(SEQ. ID NO:1373)
- 5'-CTGCCCTGGGTCT(iG-3' (FRAG. NO:1365)(SEQ. ID NO:1374)
- 5 5'-GGGTGTGGCCTTGGGGCCGTCCTCTGGCTCCTCCTCGTGGGCCCCC (FRAG.NO:1366)(SEQ.ID NO:1375)
  - 5'-GGGCTAAGAT GAICCACATC ACTACCACGT TGCCCACCAC AGAGGTCACC ACAATGACCG TGTAGGCAGC TGCCCAAAGG ACAATTTGCC AGGCTGGTTG CACGAACTGA TTGGGTTCCG AGGTGTTAGT GGAGATGTTT GGGGAGAGGT CTGAGTCCAC CGGGAGGACG TTATCCATTTC GAAGCTAGGC GGTAAAGCCC TACTATCTGTA CACAACCCCC CTCTC CAGCA GAGTCCTGTC GTGGCGCCCTG GGGCTCAGGGTCC-3'(FRAG.NO:1367)(SEO.ID NO:1376)
- 10 5'-GGGCTBBGBT GBTCCBCBTC BCTBCCBCGT TGCCCBCCBC BGBGGTCBCC BCBBTGBCCG TGTBGGCBGC TGCCCBBBGG BCBETTTGCC BGGCTGGTTG CBCGBBCTGB TTGGGTTCCG BGGTGTTBGT GGBGBTGTTT GGGGBGBGGTC TGF.GTCCBCC GGGBGGBCGT TBTCCBTTTC GBBGCTBGGC GGTBBBGCCC TBCTBTCTGTB CBCBBCCCCC CTCTG CBGCB GBGTCCTGTC GTGGCGCCTG GGGCTCBGGG TCC-3' (FRAG. NO:1369) (SEO. ID NO:1377)

#### Chymase Antisense Nucleic Acids and Oligonucleotides Antisense Oligonucleotide Fragments

20 TGGCCCTCTT CCCTCTCCTG TCTCCTGTCC CTGTGTTCCG CCCGTCTTCC

CTCTCCTGAC CTCCTTTCC TCCGCTGGGT GGGGCCCTGC CTGTTCTCTG CTCCCTGGCT TGGGGTTTCT
TCTGTGTGTC TTCTCCTCT GTTGGCTGGC TTTCTCCTTC TTTTGTCTTC CTGGGTGCCC CTTCTTCCTT
TCTTGGGTCC TTGGTGCTTG GGCTGGG TCCCAGTTAA TACATAATCA ATATGCAATT TATTAATACA
TCTCTCCATG TCCACTCCCC CTGTATCTTG CCATTCTTGA CCTGCATTTC CATCCTCCTT ACCTTCCCTA
GAGGCCAACT CATTTTCTTT GAAAAACCTG GCATTTCCCA GAAAAAAAAG TGAAGGGCTG GGAGCTGTCC
GTTGTCCTGA TTTGCTCCCT CTGCCCTTGC TTCCAAATGT GGTTGGAAAG AAGCACTATT GAAAAATCCC

TAAACGCACC CCTGCAGGGT TGGCTCTACC CTGTAGCCAT GGACACATGC TGTTGATACC ACCTGCCTCA
TGAGTCTCAC ATAATTTGCC CTTTCACACT ATCTACCCCA TCAGCCTTAC CAAAACCATA CCTGCATCCT
GGGCAGCATC TGCCCTTCAA GAGACTAAGG AATCTCCTTG CAACCAAGAA TGACTAGACC AATGAGACAC
CCTTTAAGGC CCCAGCACAA TATAGAAATC CCACAATATG GTAATCCCAG TAAGGAGCTA TCAAGCCATT
GCAGGACCAT CTAGAATACA ACTAGAGTAT AGTTCCTTTC AATCCAGGAA CTATACTCTA ACAGCTTGGC

TCACAGGAAC CAGAAGTGAA GATGATGAGG ATCAGGGCTG AGCCTGTGAG CACCAGCTCC ACCACTGACA CCAACCACAG ATTAAACAAG CATCTTGTGG ACCCCTGGGA TGGAAAGAAT AGTTGTTGCC TTATCAACCT CCCCCACAGC CCACAGAA AAGATAAAAT CATCATGGCT ACAGTGTTAC AGAAGATGAT GACCCAAGGA GTAGGCCTGC CTGAGTGAAT GCTGAGAGTG ATAATGGGAG CAGTAGCATC TCAGAGACTA CAGCAGAAAC

CATCCACATA AAGAGCTTTG CCCAAACTTA TGATAAAGGG CACCCTCAGA GACTCTCCCT ACTTTAATAT
TAGCCCATTG CAGAAATGGT GAGTGGAAAG AGAAATCTTA GGAAGAACCC CTTAAAAAAG CAAAATGCTT
TTTAGGTTTG TGCT3AAGAG CCTGGAAAAG AAATAATGCCCC
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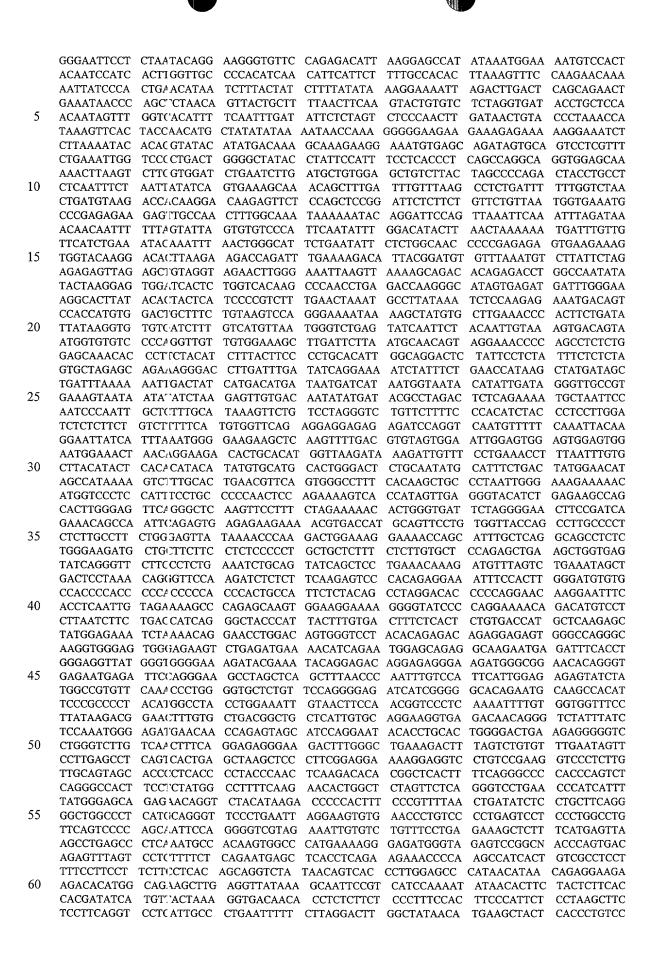
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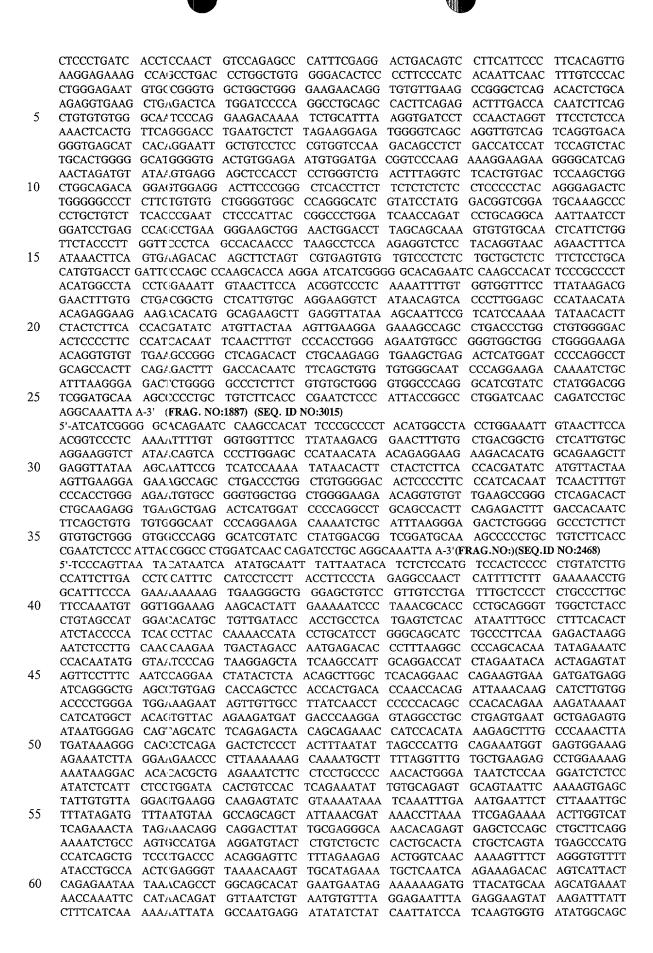
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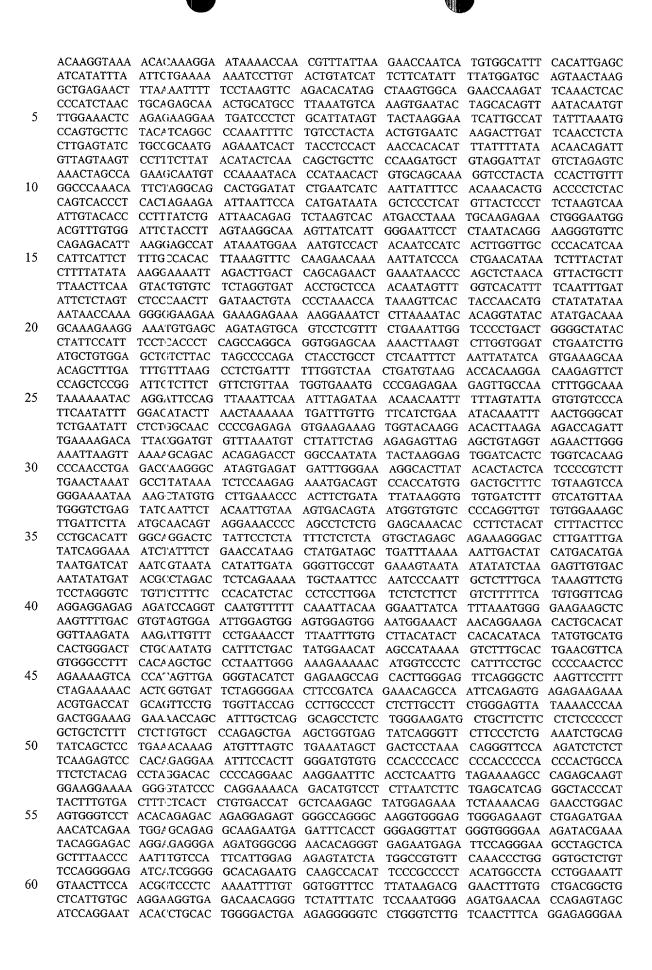
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30 5'-GGBGCBCBBG-3' (FRAG. NO:1888) (SEQ. ID NO:1901)

5'-GBBGCBGC-3' (FRAG. NO:1889) (SEQ. ID NO:1902)

5'-GGGGCBBGG CG-3' (FRAG. NO:1890) (SEQ. ID NO:1903)

5'-CGTTTTCTTCTC.3' (FRAG. NO:1369)(SEQ. ID NO:1378)

5'-GCTGGTTTTCCTTTCC-3' (FRAG. NO:1370)(SEQ. ID NO:1379)

5'-TTCCTTGTTCCTGGGGGTGTCCT-3' (FRAG. NO:1372)(SEQ. ID NO:1381)

5'-CTTGCTCTGGGCTTTTCT-3' (FRAG. NO:1373)(SEQ. ID NO:1382)

5'-CCCCTTTTCCTTCC-3' (FRAG. NO:1374)(SEQ. ID NO:1383) [

5'-TGTCTGTTTTCCTGGGG-3' (FRAG. NO:1375)(SEQ. ID NO:1384)

0 5'-CTCTCCTCTGTCTCTGTGT-3' (FRAG. NO:1376)(SEO. ID NO:1385)

5'-CCTTGCCCTGGCCC'-3' (FRAG. NO:1377)(SEQ. ID NO:1386)

5'-TCTTCCCTCTCTGTCTCCTGT-3' (FRAG. NO:1378)(SEQ. ID NO:1387)

5'-CCCTGTGTTCCGCC'C-3' (FRAG. NO:1379)(SEQ. ID NO:1388)

5'-GTCTTCCCTCTG-3' (FRAG. NO:1380)(SEQ. ID NO:1389)

5'-ACCTCCTTTTCCTCCG-3' (FRAG. NO:1381)(SEQ. ID NO:1390)

5'-CTGGGTGGGGCCC'IG-3' (FRAG. NO:1382)(SEQ. ID NO:1391)

5'-CCTGTTCTCTGCTCCC-3' (FRAG. NO:1383)(SEQ. ID NO:1392)

 $5\text{'-}TGGCTTGGGGTTTC'TTCTG-3\text{'} (FRAG.\ NO:1384) (SEQ.\ ID\ NO:1393)$ 

5'-TGTGTCTTCTTCTCTGTT-3' (FRAG. NO:1385)(SEQ. ID NO:1394)

50 5'-GGCTGGCTTTCTC('TTC-3' (FRAG. NO:1386)(SEQ. ID NO:1395)

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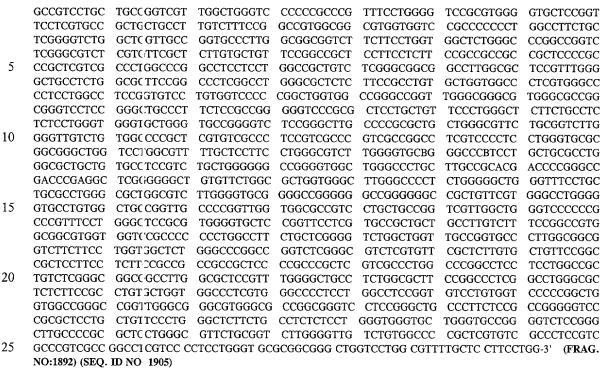
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5'-TCCTTGGTGCTTGC·GCTGGG-3' (FRAG. NO:1389)(SEQ. ID NO:1398)

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CTTTCCBGTC TTGGGTTTTB TBBCTCCCBG BBGGCBBGBG BGGGCBBGG-3' (FRAG.NO:1891) (SEQ.ID NO:1904)

#### Endothelial Nitric Oxide Synthase Nucleic Acids and Antisense Oligonucleotide Fragments

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GTGGGCTTGG GCCC'CTCTGG GGGCTGGGTT TCCTGCTGCG CCTGGGCGCT GGCGTCTTGG GGTGCGGGGC
CGGGGGGCCG GGG'3GCCGCT GTTCGTGGGC CTGGGGGTGC CTGTGGCTGC CGGTTGCCCC GGTTGGTGGC



- 5'-GCGGGGCCG-3' (FRAG. NO:1893) (SEQ. ID NO: 1906)
- 5'-CGGGGGGC-3' (FRAG. NO:1894) (SEQ. ID NO: 1907)
- 5'-GCGCGGCGGC-3' (FRAG. NO:1895) (SEQ. ID NO: 1908)
- 5°-CTGTGCGTCCGTCTGCTGG (FRAG. NO:1390)(SEQ. ID NO:1399)
  GGGGCCGGGGTGGCTGGGCCCTGCTTGCCGC (FRAG. NO:1391)(SEQ. ID NO:1400)
  ACGACCCCGGGCCGACCCGAG (FRAG. NO:1392)(SEQ. ID NO:1401)
  GCTCGGGGGGCTGTGTTCTGGCGCTGGTGGG (FRAG. NO:1393)(SEQ. ID NO:1402)
  CTTGGGCCCCTCTGGGGGCTGGGTT (FRAG. NO:1394)(SEO. ID NO:1403)
- TCCTGCTGCGCCTGGGCGCTG (FRAG. NO:1395)(SEQ. ID NO:1404)
  GCGTCTTGGGGTGC (FRAG. NO:1396)(SEQ. ID NO:1405)
  GGGGCCGGGGGGCCC GGGG (FRAG. NO:1397)(SEQ. ID NO:1406)
  GCCGCTGTTCGTGGGCCTGGG (FRAG. NO:1398)(SEQ. ID NO:1407)
  GGTGCCTGTGGCTGCC (FRAG. NO:1399)(SEQ. ID NO:1408)
- 40 GGTTGCCCCGGTTGGTGGC (FRAG. NO:1400)(SEQ. ID NO:1409)
  GCCGTCCTGCTGCCGGTT (FRAG. NO:1401)(SEQ. ID NO:1410)
  CGTTGGCTGGGTCCCCCCCC (FRAG. NO:1402)(SEQ. ID NO:1411)
  CCGTTTCCTGGGGTCC (FRAG. NO:1403)(SEQ. ID NO:1412)
  GCGTGGGGTGCTCC (FRAG. NO:1404)(SEQ. ID NO:1413)
- 45 GGTTCCTCGTGCCG (I'RAG. NO:1405)(SEQ. ID NO:1414)
  CTGCTGCCTTGTCTTTCC (FRAG. NO:1406)(SEQ. ID NO:1415)
  GGCCGTGGCGGCGTGGTGGTCC (FRAG. NO:1407)(SEQ. ID NO:1416)
  GCCCCCCCTGGCCTTCTGCTC (FRAG. NO:1408)(SEQ. ID NO:1417)
  GGGGTCTGGCTGGT (\*RAG. NO:1409)(SEQ. ID NO:1418)
- 50 TGCCGGTGCCCTTGGCGGC (FRAG. NO:1410)(SEQ. ID NO:1419)
  GGTCTTCTTCCTGGTC; (FRAG. NO:1411)(SEQ. ID NO:1420)
  GCTCTGGGCCCGGCC3GTCTCGG (FRAG. NO:1412)(SEQ. ID NO:1421)
  GCGTCTCGTGTTCG (FRAG. NO:1413)(SEQ. ID NO:1422)
  CTCTTGTGCTGTTCCCGCCG (FRAG. NO:1414)(SEQ. ID NO:1423)
- 55 CTCCTTCCTCTCCGC CGCC (FRAG. NO:1415)(SEQ. ID NO:1424)
  GCCGCTCCCCGCCC (FRAG. NO:1416)(SEQ. ID NO:1425)
  GCTCGTCGCCCTGGCCC (FRAG. NO:1417)(SEQ. ID NO:1426)
  GGCCTCCTCCTGGCCGC (FRAG. NO:1418)(SEQ. ID NO:1427)
  TGTCTCGGGCGGCGCTTTGGC (FRAG. NO:1419)(SEQ. ID NO:1428)
  60 GCTCCGTTTGGGGCTG (FRAG. NO:1420)(SEQ. ID NO:1429)

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15

TCTTCCGCCTGTGC (FRAG. NO:1423)(SEQ. ID NO:1432) TGGTGGCCCTCGTGG (FRAG. NO:1424)(SEQ. ID NO:1433) GCCCCTCCTGGCCTCCGGTGTCC (FRAG. NO:1425)(SEQ. ID NO:1434) TGTGGTCCCCCGGCTGGT (FRAG. NO:1426)(SEQ. ID NO:1435) GGCCGGGCCGGTTGGGCGGGC (FRAG. NO:1427)(SEQ. ID NO:1436) GTGGGCGCGGGGTCCTCC (FRAG. NO:1428)(SEQ. ID NO:1437) GGGCTGCCCTTCTCC (FRAG. NO:1429)(SEQ. ID NO:1438) GCCGGGGGTCCCGC (FRAG. NO:1430)(SEQ. ID NO:1439) GCTCCTGCTGTTCCCTGGGCTCTTCTGCC (FRAG. NO:1431)(SEQ. ID NO:1440) TCTCTCCTGGGTGGG' GCTGGGTGCCG (FRAG. NO:1432)(SEQ. ID NO:1441) GGGTCTCCGGGCTTG (FRAG. NO:1433)(SEO. ID NO:1442) CCCCGCGCTGCTGGGCGTTCTGC (FRAG. NO:1434)(SEO. ID NO:1443) GGTCTTGGGGTTGTC (FRAG. NO:1435)(SEQ. ID NO:1444) TGTGGCCCCGCTCG (J'RAG, NO:1436)(SEQ, ID NO:1445) TGTCGCCCTCCGTCGCC (FRAG. NO:1437)(SEQ. ID NO:1446) CGTCGCCGGCCTCGTCC (FRAG. NO:1438)(SEQ. ID NO:1447) CCTCCTGGGTGCGC (JiRAG, NO:1439)(SEQ, ID NO:1448) GGCGGGCTGGTCCT (7RAG. NO:1440)(SEQ. ID NO:1449)

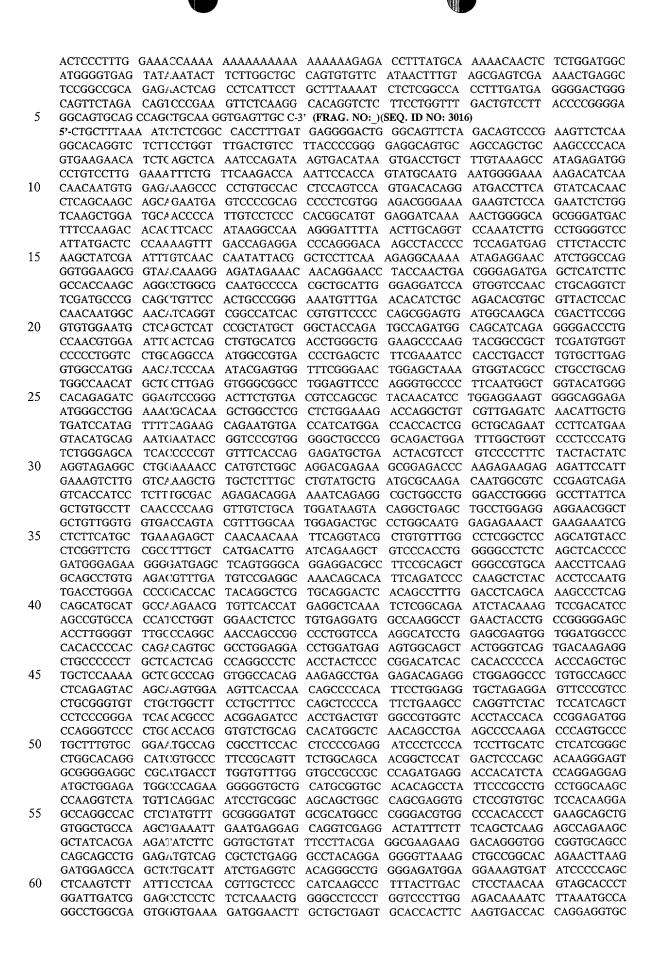
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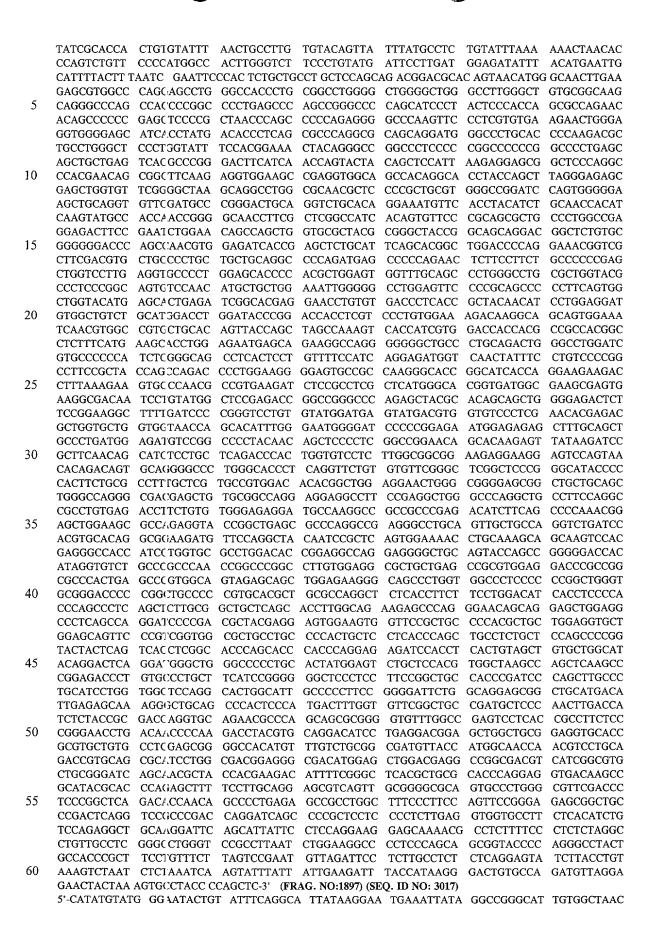
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## Inducible Nitric Oxide Synthase Nucleic Acids and Antisense Oligonucleotide Fragments

267

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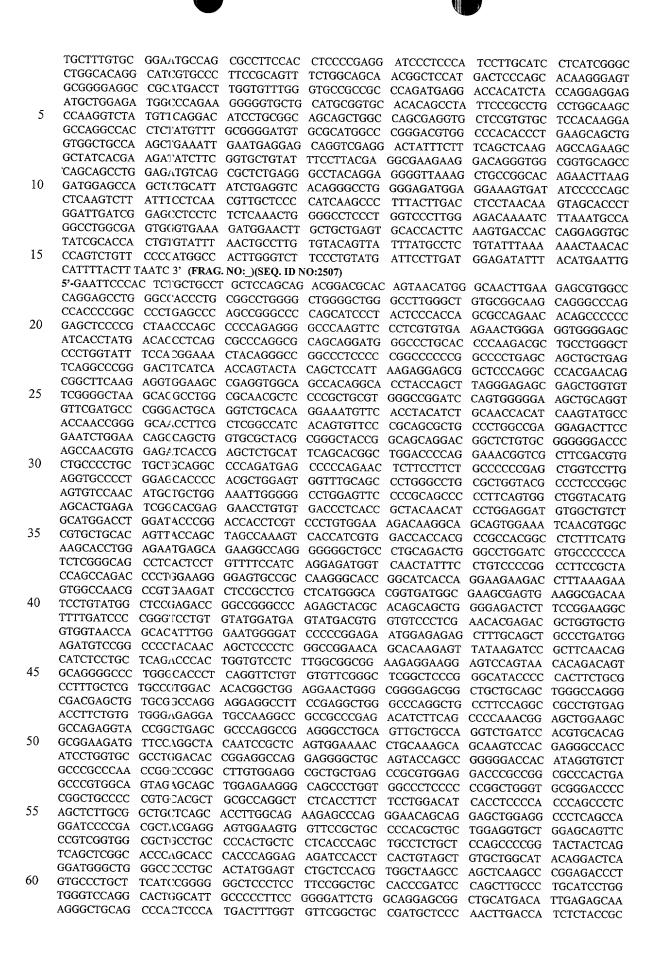
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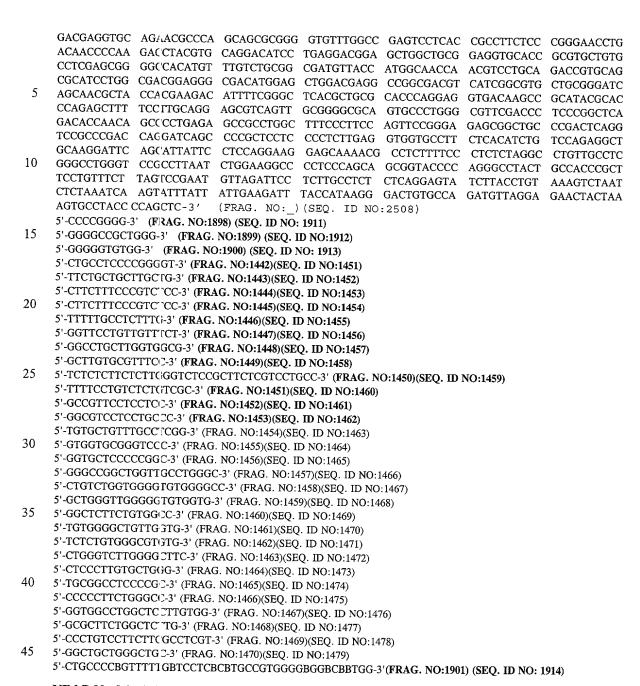
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### NF-kB Nucleic Aci ls and Antisense Oligonucleotide Fragments

60 5'-GGGCGGGGTCGC-3' (FRAG. NO:1903) (SEQ. ID NO:1916) 5'-GCGCCGTCC-3' (FRAG. NO:1904) (SEQ. ID NO:1917)

- 5'-GGGCGTGGTGG-3' (FRAG. NO:1905) (SEQ. ID NO:1918) 5'-GTTGGGCTTGGCCGGGG-3' (FRAG. NO:1471)(SEQ. ID NO:1480) 5'-CTGCCCGGTGCCTCC-3' (FRAG. NO:1472)(SEQ. ID NO:1481) 5'-TCTTGGCTGGTCCCTCGT-3' (FRAG. NO:1473)(SEO. ID NO:1482) 5'-TGTCCTTGGGCCCC-3' (FRAG. NO:1474)(SEQ. ID NO:1483) 5'-GCTCCCGCTGCTCGGCCTCCGT-3' (FRAG. NO:1475)(SEQ. ID NO:1484) 5'-GTTCTTTGGCCTC'ITGCTCC-3' (FRAG. NO:1476)(SEQ. ID NO:1485) 5'-GCCTGCTGTCTTGTCC-3' (FRAG. NO:1477)(SEQ. ID NO:1486) 5'-CGTCCCCTCCTCGCTTTGCGTTTC-3' (FRAG. NO:1478)(SEQ. ID NO:1487) 5'-CCTCTTCCTTGTC' TCCA-3' (FRAG. NO:1479)(SEQ. ID NO:1488) 5'-GGCCTTCCTCCGCTCCGCTGC-3' (FRAG. NO:1480)(SEQ. ID NO:1489) 5'-TGGGGCCCGCGCGG-3' (FRAG. NO:1481)(SEQ. ID NO:1490) 5'-GGGGGCGCTCCGCGGCTTCCTCCCCGG-3' (FRAG. NO:1482)(SEQ. ID NO:1491) 5'-CTGGGGGGTCCTGG-3' (FRAG. NO:1483)(SEQ. ID NO:1492) 5'-TCTCCGGGGCCTGCGGCTCGC-3' (FRAG. NO:1484)(SEQ. ID NO:1493) 5'-GGGCTCGGGGCTGCGCCC-3' (FRAG. NO:1485)(SEQ. ID NO:1494) 5'-GCGCGCGCGTCCGCGGTG-3' (FRAG. NO:1486)(SEQ. ID NO:1495) 5'-GGTGGCGCTGTCCCGCC-3' (FRAG. NO:1487)(SEQ. ID NO:1496) 5'-GTGGTGTCTCCGTCCTGCGCCGTC-3' (FRAG. NO:1488)(SEQ. ID NO:1497) 5'-CTGGTCTGCCCGTGG-3' (FRAG. NO:1489)(SEQ. ID NO:1498) 5'-GGTCCTGGGCGTGGTGG-3' (FRAG. NO:1490)(SEQ. ID NO:1499) 5'-GGGGCGTCTGGTGC-3' (FRAG. NO:1491)(SEQ. ID NO:1500) 5'-CTCGTCTGCCCCG'[G-3' (FRAG. NO:1492)(SEQ. ID NO:1501) 5'-GGGCTTCGGGCTC 3G-3' (FRAG. NO:1493)(SEQ. ID NO:1502) 5'-GGCTGTTCGTCCCCCCCCCCCCCCTGTGGCCTCC-3' (FRAG. NO:1494)(SEQ. ID NO:1503) 5'-GGGGCTCCTCGTT'[TC-3' (FRAG. NO:1495)(SEQ. ID NO:1504) 5'-GCTGCTTCGGGTG'ICCTTCTC-3' (FRAG. NO:1496)(SEQ. ID NO:1505) 5'-GGCGTGTGGCCCC3G-3' (FRAG. NO:1497)(SEQ. ID NO:1506) 5'-GTCCCGGCCCTGC'IGGGCTGGGCGGGGTC-3' (FRAG. NO:1498)(SEQ. ID NO:1507) 5'-GCTGCCCTGGGCT'ICTGGCCCGTCT-3' (FRAG. NO:1499)(SEQ. ID NO:1508) 5'-GGTTGTCTGTCGG' '-3' (FRAG. NO:1500)(SEO. ID NO:1509) 5'-GCTTGTCTCGGGT' TCTGG-3' (FRAG. NO:1501)(SEQ. ID NO:1510) 5'-CCTCTGTGCTGGGC-3' (FRAG. NO:1502)(SEQ. ID NO:1511) 5'-GCTTCTCTGCCTCC'TGCTCC-3' (FRAG. NO:1503)(SEQ. ID NO:1512) 5'-GCCCTCCTGGTGGCTC-3' (FRAG. NO:1504)(SEQ. ID NO:1513) 5'-GGCTGGGGTGCCCGTGCG-3' (FRAG. NO:1505)(SEQ. ID NO:1514) 5'-GGGGTGGGGTGTT-3' (FRAG. NO:1506)(SEQ. ID NO:1515) 5'-TTCGGGGTCCTCCCCTTCCC-3' (FRAG. NO:1507)(SEQ. ID NO:1516) 5'-CGGCCCTTCTCACT'GGAGGCACCGGGCAGTCCTCCATGGGAGG-3' (FRAG.NO:1906)(SEQ.ID NO:1919) Human Major Basic Protein Nucleic Acids and Antisense Oligonucleotide Fragments

5'-GTT TCA TCT TGG CTT TAT CCTCT CCC CTT GTT CCT CCC CTCT CCT GCT CTG GRG TCT CCT C TTC CCT GGA GTT TCA TCT T3G GTT TCB TCT TGG CTT TBT CCTCT CCC CTT GTT CCT CCC CTCT CCT GCT CTG GRG 

CCC TGC TGG GGG GGB GTT TCB TCT TGG-3' (FRAG. ID:1907) (SEQ. ID NO:1920)

5'-GGG GGA GTT-3' (FRAG. ID:1908) (SEQ. ID NO:1921)

5'-G CCC TGG GCC C-3' (FRAG. ID:1909) (SEQ. ID NO:1922)

5'-GTT TCA TCT TGG CTT TAT CC-3' (FRAG. NO:1508) (SEQ. ID NO:1517)

5'-TCT CCC CTT GTT CCT CCC C-3' (FRAG. NO:1509)(SEQ. ID NO:1518)

5'-TCT CCT GCT CTG 3RG TCT CCT C-3' (FRAG. NO:1510)(SEQ. ID NO:1519)

5'-TTC CCT CCC TCC CCT GCC-3' (FRAG. NO:1511)(SEQ. ID NO:1520)

5'-GTG TTG TCT GTG GGT GTC C-3' (FRAG. NO:1512)(SEQ. ID NO:1521)

5'-GTT TCG CTC TTG 'ITG CCC-3' (FRAG. NO:1513)(SEO. ID NO:1522)

5'-TGG GCC CTT CCC TGC TGG-3' (FRAG. NO:1514)(SEQ. ID NO:1523)

5'-GGG GGA GTT TCA TCT TGG-3' (FRAG. NO:1515)(SEQ. ID NO:1524)

5'-GTT TCA TCT TGG CTT TAT CCTCT CCC CTT GTT CCT CCC CTCT CCT GCT CTG GRG TCT CCT C TTC CCT GGA GTT TCA TCT TCG-3' (FRAG. ID:1910) (SEQ. ID NO:1923)

5'-GTT TCB TCT TGG CTT TBT CCTCT CCC CTT GTT CCT CCC CTCT CCT GCT CTG GRG TCT CCT C TTC CCT CCC 60 

GTT TCB TCT TGG-3' (FRAG. ID:1911) (SEQ. ID NO:1924)

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# Human Eosinophi | Major Basic Protein Nucleic Acids and Antisense Oligonucleotide Fragments

5'-GGG GGB GTT TCI: TCT TGG-3' (FRAG. NO:1519)(SEQ. ID NO: 1528)
5'-GGG GGB GTT TCI: TCT TGG CT-3' (FRAG. NO:1517)(SEQ. ID NO: 1526)
5'-GGG GGB GTT TCI: TCT TGG CT-3' (FRAG. NO:1517)(SEQ. ID NO: 1526)
5'-GGG GGB GTT TCI: TCT TGG CT-3' (FRAG. NO:1518)(SEQ. ID NO: 1527)
5'-GGG GGB GTT TCI: TCT TGG-3' (FRAG. NO:1529)(SEQ. ID NO: 1528)
5'-GGG GGB GTT TCI: TCT TG-3' (FRAG. NO:1520)(SEQ. ID NO: 1530)
5'-GGG GGB GTT TCI: TCT T-3' (FRAG. NO:1522)(SEQ. ID NO: 1531)
5'-GGG GGB GTT TCI: TCT-3' (FRAG. NO:1523)(SEQ. ID NO: 1532)
5'-GGG GGB GTT TCI: TC-3' (FRAG. NO:1524)(SEQ. ID NO: 1533)
5'-GGG GGB GTT TCI: TC-3' (FRAG. NO:1525)(SEQ. ID NO: 1534)
5'-GGG GGB GTT TCI: T-3' (FRAG. NO:1526)(SEQ. ID NO: 1535)

5'-GGG GGB GTT TCI: T-3' (FRAG. NO:1525)(SEQ. ID NO: 1534)
5'-GGG GGB GTT TCI:-3' (FRAG. NO:1526)(SEQ. ID NO: 1535)
5'-GG GGB GTT TCB TCT TGG CTT T-3' (FRAG. NO:1527)(SEQ. ID NO: 1536)
5'-GG GGB GTT TCB TCT TGG CTT-3' (FRAG. NO:1528)(SEQ. ID NO: 1537)

5'-GG GGB GTT TCB 'TCT TGG CT-3' (FRAG. NO:1529)(SEQ. ID NO: 1538)
 5'-GG GGB GTT TCB 'TCT TGG C-3' (FRAG. NO:1530)(SEQ. ID NO: 1539)
 5'-GG GGB GTT TCB 'TCT TGG-3' (FRAG. NO:1531)(SEQ. ID NO: 1540)
 5'-GG GGB GTT TCB 'TCT TG-3' (FRAG. NO:1532)(SEQ. ID NO: 1541)
 5'-GG GGB GTT TCB 'TCT T-3' (FRAG. NO:1533)(SEQ. ID NO: 1542)

20 5'-GG GGB GTT TCB 'CT-3' (FRAG. NO:1534)(SEQ. ID NO: 1543)
5'-GG GGB GTT TCB 'C-3' (FRAG. NO:1535)(SEQ. ID NO: 1544)
5'-GG GGB GTT TCB 'C-3' (FRAG. NO:1536)(SEQ. ID NO: 1545)
5'-G GGB GTT TCB TCT TGG CTT T-3' (FRAG. NO:1537)(SEQ. ID NO: 1546)
5'-G GGB GTT TCB TCT TGG CTT-3' (FRAG. NO:1538)(SEQ. ID NO: 1547)

25 5'-G GGB GTT TCB TCT TGG CT-3' (FRAG. NO:1539)(SEQ. ID NO: 1548)
5'-G GGB GTT TCB TCT TGG C-3' (FRAG. NO:1540)(SEQ. ID NO: 1549)
5'-G GGB GTT TCB TCT TGG-3' (FRAG. NO:1541)(SEQ. ID NO: 1550)
5'-G GGB GTT TCB TCT TG-3' (FRAG. NO:1542)(SEQ. ID NO: 1551)
5'-G GGB GTT TCB TCT T-3' (FRAG. NO:1543)(SEQ. ID NO: 1552)

5'-G GGB GTT TCB TC T-3' (FRAG. NO:1544)(SEQ. ID NO: 1553)
5'-G GGB GTT TCB TC -3' (FRAG. NO:1545)(SEQ. ID NO: 1554)
5'-GGB GTT TCB TCT TGG CTT T-3' (FRAG. NO:1546)(SEQ. ID NO: 1555)
5'-GGB GTT TCB TCT TGG CTT-3' (FRAG. NO:1547)(SEQ. ID NO: 1556)
5'-GGB GTT TCB TCT TGG CT-3' (FRAG. NO:1548)(SEQ. ID NO: 1557)

5'-GGB GTT TCB TCT TGG C-3' (FRAG. NO:1549)(SEQ. ID NO: 1558)
 5'-GGB GTT TCB TCT TGG-3' (FRAG. NO:1550)(SEQ. ID NO: 1559)
 5'-GGB GTT TCB TCT TG-3' (FRAG. NO:1551)(SEQ. ID NO: 1560)
 5'-GGB GTT TCB TCT T-3' (FRAG. NO:1552)(SEQ. ID NO: 1561)
 5'-GGB GTT TCB TCT-3' (FRAG. NO:1553)(SEQ. ID NO: 1562)

5'-GB GTT TCB TCT T'GG CTT T-3' (FRAG. NO:1554)(SEQ. ID NO: 1563)
 5'-GB GTT TCB TCT T'GG CTT-3' (FRAG. NO:1555)(SEQ. ID NO: 1564)
 5'-GB GTT TCB TCT T'GG CT-3' (FRAG. NO:1556)(SEQ. ID NO: 1565)
 5'-GB GTT TCB TCT T'GG C-3' (FRAG. NO:1557)(SEQ. ID NO: 1566)
 5'-GB GTT TCB TCT T'GG-3' (FRAG. NO:1558)(SEQ. ID NO: 1567)

5'-GB GTT TCB TCT Tig-3' (FRAG. NO:1559)(SEQ. ID NO: 1568)
5'-GB GTT TCB TCT Tig' (FRAG. NO:1560)(SEQ. ID NO: 1569)
5'-B GTT TCB TCT Tig' CTT T-3' (FRAG. NO:1561)(SEQ. ID NO: 1570)
5'-B GTT TCB TCT Tig' CTT-3' (FRAG. NO:1562)(SEQ. ID NO: 1571)
5'-B GTT TCB TCT Tig' CTT-3' (FRAG. NO:1563)(SEQ. ID NO: 1572)

5'-B GTT TCB TCT TGG CT-3' (FRAG. NO:1564)(SEQ. ID NO: 1573)
5'-B GTT TCB TCT TGG C-3' (FRAG. NO:1565)(SEQ. ID NO: 1574)
5'-B GTT TCB TCT TGG-3' (FRAG. NO:1565)(SEQ. ID NO: 1575)
5'-B GTT TCB TCT TG-3' (FRAG. NO:1567)(SEQ. ID NO: 1576)
5'-GTT TCB TCT TGG CTT T-3' (FRAG. NO:1568)(SEQ. ID NO: 1577)

5'-GTT TCB TCT TGG (CTT-3' (FRAG. NO:1569)(SEQ. ID NO: 1577)
5'-GTT TCB TCT TGG (CT-3' (FRAG. NO:1569)(SEQ. ID NO: 1578)
5'-GTT TCB TCT TGG (C-3' (FRAG. NO:1571)(SEQ. ID NO: 1580)
5'-GTT TCB TCT TGG-C' (FRAG. NO:1572)(SEQ. ID NO: 1581)
5'-TT TCB TCT TGG C'T T-3' (FRAG. NO:1574)(SEQ. ID NO: 1582)
5'-TT TCB TCT TGG C'T-3' (FRAG. NO:1574)(SEQ. ID NO: 1583)

5'-TT TCB TCT TGG CT'-3' (FRAG. NO:1574)(SEQ. ID NO: 1583) 5'-TT TCB TCT TGG CT'-3' (FRAG. NO:1575)(SEQ. ID NO: 1584)

5'-TT TCB TCT TGG C-3' (FRAG. NO:1576)(SEQ. ID NO: 1585) 5'-T TCB TCT TGG C"T T-3' (FRAG. NO:1577)(SEQ. ID NO: 1586) 5'-T TCB TCT TGG C'T-3' (FRAG. NO:1578)(SEQ. ID NO: 1587) 5'-T TCB TCT TGG C'-3' (FRAG. NO:1579)(SEQ. ID NO: 1588) 5'-TCB TCT TGG CTT T-3' (FRAG. NO:1580)(SEQ. ID NO: 1589) 5'-TCB TCT TGG CTT-3' (FRAG. NO:1581)(SEQ. ID NO: 1590) 5'-GGG GGB GTT TCI; TCT TGG CTT T-3' (FRAG. NO:1582)(SEQ. ID NO:1591) 5'-GG GGB GTT TCB 'TCT TGG CTT T-3' (FRAG. NO:1583)(SEQ. ID NO: 1592) 5'-G GGB GTT TCB TCT TGG CTT T-3' (FRAG. NO:1584)(SEQ. ID NO: 1593) 5'-GGB GTT TCB TCT TGG CTT T-3' (FRAG. NO:1585)(SEQ. ID NO: 1594) 5'-GB GTT TCB TCT T'GG CTT T-3' (FRAG. NO:1586)(SEO. ID NO: 1595) 5'-B GTT TCB TCT TC G CTT T-3' (FRAG. NO:1587)(SEO. ID NO: 1596) 5'-GTT TCB TCT TGG CTT T-3' (FRAG. NO:1588)(SEQ. ID NO: 1597) 5'-TT TCB TCT TGG ('TT T-3' (FRAG. NO:1589)(SEQ. ID NO: 1598) 5'-T TCB TCT TGG Cl'T T-3' (FRAG. NO:1590)(SEQ. ID NO: 1599) 5'-TCB TCT TGG CTT T-3' (FRAG. NO:1591)(SEQ. ID NO: 1600) 5'-CB TCT TGG CTT 7-3' (FRAG. NO:1592)(SEQ. ID NO: 1601)  $5^{\circ}\text{-}GGG\ GGB\ GTT\ TCF\ TCT\ TGG\ CTT-3^{\circ}\ (FRAG.\ NO:1593)(SEQ.\ ID\ NO:\ 1602)$ 5'-GG GGB GTT TCB 'CT TGG CTT-3' (FRAG. NO:1594)(SEQ. ID NO: 1603) 5'-G GGB GTT TCB TCT TGG CTT-3' (FRAG. NO:1595)(SEQ. ID NO: 1604) 5'-GGB GTT TCB TCT TGG CTT-3' (FRAG. NO:1596)(SEO. ID NO: 1605) 5'-GB GTT TCB TCT TGG CTT-3' (FRAG. NO:1597)(SEQ. ID NO: 1606) 5'-B GTT TCB TCT TGG CTT-3' (FRAG. NO:1598)(SEO. ID NO: 1607) 5'-GTT TCB TCT TGG CTT-3' (FRAG. NO:1599)(SEQ. ID NO: 1608) 5'-TT TCB TCT TGG CTT-3' (FRAG. NO:1600)(SEQ. ID NO: 1609) 5'-T TCB TCT TGG CTT-3' (FRAG. NO:1601)(SEQ. ID NO: 1610) 5'-TCB TCT TGG CTT 3' (FRAG. NO:1602)(SEQ. ID NO: 1611) 5'-GGG GGB GTT TCB TCT TGG CT-3' (FRAG. NO:1603)(SEQ. ID NO: 1612) 5'-GG GGB GTT TCB 1'CT TGG CT-3' (FRAG. NO:1604)(SEQ. ID NO: 1613) 5'-G GGB GTT TCB TCT TGG CT-3' (FRAG. NO:1605)(SEQ. ID NO: 1614) 5'-GGB GTT TCB TCT TGG CT-3' (FRAG. NO:1606)(SEQ. ID NO: 1615) 5'-GB GTT TCB TCT TGG CT-3' (FRAG. NO:1607)(SEQ. ID NO: 1616) 5'-B GTT TCB TCT TGG CT-3' (FRAG. NO:1608)(SEQ. ID NO: 1617) 5'-GTT TCB TCT TGG CT-3' (FRAG. NO:1609)(SEQ. ID NO: 1618) 5'-TT TCB TCT TGG CT-3' (FRAG. NO:1610)(SEQ. ID NO: 1619) 5'-T TCB TCT TGG CT-3' (FRAG. NO:1611)(SEQ. ID NO: 1620) 5'-GGG GGB GTT TCB TCT TGG C-3' (FRAG. NO:1612)(SEQ. ID NO: 1621) 5'-GG GGB GTT TCB TCT TGG C-3' (FRAG. NO:1613)(SEQ. ID NO: 1622) 5'-G GGB GTT TCB TCT TGG C-3' (FRAG. NO:1614)(SEQ. ID NO: 1623) 5'-GGB GTT TCB TCT TGG C-3' (FRAG. NO:1615)(SEQ. ID NO: 1624) 5'-GB GTT TCB TCT T3G C-3' (FRAG. NO:1616)(SEQ. ID NO: 1625) 5'-B GTT TCB TCT TG 3 C-3' (FRAG. NO:1617)(SEQ. ID NO: 1626) 5'-GTT TCB TCT TGG C-3' (FRAG. NO:1618)(SEO. ID NO: 1627) 5'-TT TCB TCT TGG C-3' (FRAG. NO:1619)(SEQ. ID NO: 1628) 5'-GGG GGB GTT TCB TCT TGG-3' (FRAG. NO:1620)(SEO. ID NO: 1629) 5'-GG GGB GTT TCB TCT TGG-3' (FRAG. NO:1621)(SEQ. ID NO: 1630) 5'-G GGB GTT TCB TCT TGG-3' (FRAG. NO:1622)(SEQ. ID NO: 1631) 5'-GGB GTT TCB TCT TGG-3' (FRAG. NO:1623)(SEQ. ID NO: 1632) 5'-GB GTT TCB TCT T'3G-3' (FRAG. NO:1624)(SEQ. ID NO: 1633) 5'-B GTT TCB TCT TG/G-3' (FRAG. NO:1625)(SEQ. ID NO: 1634) 5'-GTT TCB TCT TGG-3' (FRAG. NO:1626)(SEQ. ID NO: 1635) 5'-GGG GGB GTT TCB TCT TG-3' (FRAG. NO:1627)(SEQ. ID NO: 1636) 5'-GG GGB GTT TCB TCT TG-3' (FRAG. NO:1628)(SEQ. ID NO: 1637) 5'-G GGB GTT TCB TCT TG-3' (FRAG. NO:1629)(SEQ. ID NO: 1638) 5'-GGB GTT TCB TCT 'FG-3' (FRAG. NO:1630)(SEQ. ID NO: 1639) 5'-GB GTT TCB TCT TG-3' (FRAG. NO:1631)(SEQ. ID NO: 1640) 5'-B GTT TCB TCT TG-3' (FRAG. NO:1632)(SEQ. ID NO: 1641) 5'-GGG GGB GTT TCB TCT T-3' (FRAG. NO:1633)(SEQ. ID NO: 1642)

5'-GG GGB GTT TCB TCT T-3' (FRAG. NO:1634)(SEQ. ID NO: 1643)
5'-G GGB GTT TCB TCT T-3' (FRAG. NO:1635)(SEQ. ID NO: 1644)
5'-G GGB GTT TCB TCT T-3' (FRAG. NO:1636)(SEQ. ID NO: 1645)
5'-GGB GTT TCB TCT '[-3' (FRAG. NO:1637)(SEQ. ID NO: 1646)

5'-GB GTT TCB TCT 1-3' (FRAG. NO:1638)(SEO. ID NO: 1647) 5'-GGG GGB GTT TCE TCT-3' (FRAG. NO:1639)(SEQ. ID NO: 1648) 5'-GG GGB GTT TCB "CT-3" (FRAG. NO:1640)(SEQ. ID NO: 1649) 5'-G GGB GTT TCB TCT-3' (FRAG. NO:1641)(SEQ. ID NO: 1650) 5'-GGB GTT TCB TCT 3' (FRAG. NO:1642)(SEQ. ID NO: 1651) 5'-GGG GGB GTT TCE TC-3' (FRAG. NO:1643)(SEQ. ID NO: 1652) 5'-GG GGB GTT TCB  $\ensuremath{\text{TC-3'}}$  (FRAG. NO:1644)(SEQ. ID NO: 1653) 5'-G GGB GTT TCB T('-3' (FRAG. NO:1645)(SEQ. ID NO: 1654) 5'-GGG GGB GTT TCB T-3' (FRAG. NO:1646)(SEQ. ID NO: 1655) 5'-GG GGB GTT TCB T-3' (FRAG. NO:1647)(SEQ. ID NO: 1656) 5'-GGG GGB GTT TCB-3' (FRAG. NO:1648)(SEQ. ID NO: 1657) 5'-TCT CCC CTT GTT CCT CCC C-3' (FRAG. NO:1649)(SEO. ID NO: 1658) 5'-TCT CCT GCT CTG GTG TCT CCT C-3' (FRAG. NO:1650)(SEO. ID NO: 1659) 5'-TTC CCT CCC TCC CCT GCC-3' (FRAG. NO:1651)(SEQ. ID NO:1660) 5'-GTG TTG TCT GTG GGT GTC C-3' (FRAG. NO:1652)(SEQ. ID NO: 1661) 5'-GTT TCG CTC TTG TTG CCC-3' -3' (FRAG. NO:1653)(SEQ. ID NO: 1661) 5'-TGG GCC CTT CCC TGC TGG-3' (FRAG. NO:1654)(SEQ. ID NO: 1663) 5'-GGG GGB G-3' (FRAG. NO:1912)(SEQ. ID NO:1925) 5'-GTG GGT GTC C-3' (FRAG. NO:1913) (SEQ. ID NO: 1926)

# **BP-1 Nucleic Acids and Antisense Oligonucleotide Fragments**

5'-CCGTGTTGTC BGTGGTGCTG CCCGTTTGBG GTBTGGCGCT CCBCCBBTTC CCTTTTCTCC TTGTTTTCCG TTTCTCTTGC CGTCTGTGGT T-3' (FRAG. NO:1914) (SEQ. ID NO: 1927) 5'-CCCGTTTGBGGTBTGGC-3'(FRAG. NO:1915) (SEQ. ID NO: 1928)

5'-GCTCCBCCBBTTCCCTTTTCTCC-3'(FRAG. NO:1916) (SEQ. ID NO: 1929)

5'-TTGTTTTCCGTTTC CTTG-3'(FRAG. NO:1917) (SEO. ID NO: 1930)

5'-CCGTCTGTGGTT-3'(FRAG. NO:1918) (SEQ. ID NO: 1931)

5'-CCCGTTTGAGGTATGGC-3'(FRAG. NO:1919) (SEQ. ID NO: 1932)

5'-GCTCCBCCAATTCCCTTTTCTCC-3'(FRAG. NO:1920) (SEQ. ID NO: 1933)

# C/EBPNucleic Acicls and Antisense Oligonucleotide Antisense Oligonucleotide Fragments

5'-GGGCCCBGCCCGCCGCCTTTTCTBGCCCC GGCC-3' (FRAG. NO:1921) (SEQ. ID NO: 1934)

5'-GGGCCCBGCCCGCCTTTTCTBGCCCC GGC-3' (FRAG. NO:1922) (SEQ. ID NO: 1935)

5'-GGGCCCB GCCCGCCGCCTTTTCTBGCCCCGG-3' (FRAG. NO:1923) (SEQ. ID NO: 1936)

5'-GGGCCCBGCCCGCCCTTTTCTBGCCCCG-3' (FRAG. NO:1924) (SEQ. ID NO: 1937)

5'-GGGCCCBGCCCGCCTTTTCTBGCCCC-3' (FRAG. NO:1925) (SEQ. ID NO: 1938)

5'-GGGCCCBGCCCGCCGCTTTTCTBGCCC-3' (FRAG. NO:1926) (SEQ. ID NO: 1939)

5'-GGGCCCBGCCCGCCGCCTTTTCTBGCC-3' (FRAG. NO:1927) (SEQ. ID NO: 1940)

5'-GGGCCCBGCCCGCCGCCTTTTCTBGC-3' (FRAG. NO:1928) (SEO. ID NO: 1941) 5'-GGGCCCBGCCCGCCTTTTCTBG-3' (FRAG. NO:1929) (SEQ. ID NO: 1942)

5'-GGGCCCBGCCCGCCCTTTTCTB-3' (FRAG. NO:1930) (SEQ. ID NO: 1943)

5'-GGGCCCBGCCCGCCGCTTTTCT-3' (FRAG. NO:1931) (SEQ. ID NO:1942) 1944)

5'-GGGCCCBGCCCGCCGCTTTTC-3' (FRAG. NO:1932) (SEQ. ID NO: 1945) 5'-GGGCCCBGCCCGCCGCCTTTT-3' (FRAG. NO:1933) (SEQ. ID NO: 1946)

5'-GGGCCCBGCCCGCCGCCTTT-3' (FRAG. NO:1934) (SEQ. ID NO: 1947) [1945)]

5'-GGGCCCBGCCCGCCGCTT-3' (FRAG. NO:1935) (SEQ. ID NO: 1948)

5'-GGGCCCBGCCCGCCGCCT-3' (FRAG. NO:1936) (SEQ. ID NO: 1949)

5'-GGGCCCBGCCCGCCGCC-3' (FRAG. NO:1937) (SEQ. ID NO: 1950)

5'-GGGCCCBGCCCGCCGC-3' (FRAG. NO:1938) (SEQ. ID NO: 1951)

5'-GGGCCCBGCCCGCCG-3' (FRAG. NO:1939) (SEQ. ID NO: 1952)

5'-GGGCCCBGCCCGCC-3' (FRAG. NO:1940) (SEQ. ID NO: 1953)

50 5'-GGGCCCBGCCCGC-3' (FRAG. NO:1941) (SEQ. ID NO: 1954)

5'-GGGCCCBGCCCCG-3' (FRAG. NO:1942) (SEO. ID NO: 1955)

5'-GGGCCCBGCCCC-3' (FRAG. NO:1943) (SEQ. ID NO: 1956)

5'-GGGCCCBGCCC-3' (FRAG. NO:1944) (SEQ. ID NO: 1957)

5'-GGCCCBGCCCGCCGCCTTTTCTBGCCCCGGC-3' (FRAG. NO:1945) (SEQ. ID NO: 1958)

5'-GCCCBGCCCGCCGCCGCCTTTTCTBGCCCCGGC-3' (FRAG. NO:1946) (SEQ. ID NO: 1959)

5'-CCCBGCCCGCCGCCTTTTCTBGCCCCGGC-3' (FRAG. NO:1947) (SEQ. ID NO: 1960)

5'-CCBGCCCGCCGCC'TTTTCTBGCCCCGGC-3' (FRAG. NO:1948) (SEQ. ID NO: 1961)

5'-CBGCCCGCCCTTTTCTBGCCCCGGC-3' (FRAG. NO:1948) (SEQ. ID NO: 1962)

5'-BGCCCCGCCGCCTTTTCTBGCCCCGGC-3' (FRAG. NO:1950) (SEQ. ID NO: 1963)

5'-GCCCCGCCGCCTTTTCTBGCCCCGGC-3' (FRAG. NO:1951) (SEQ. ID NO: 1964)

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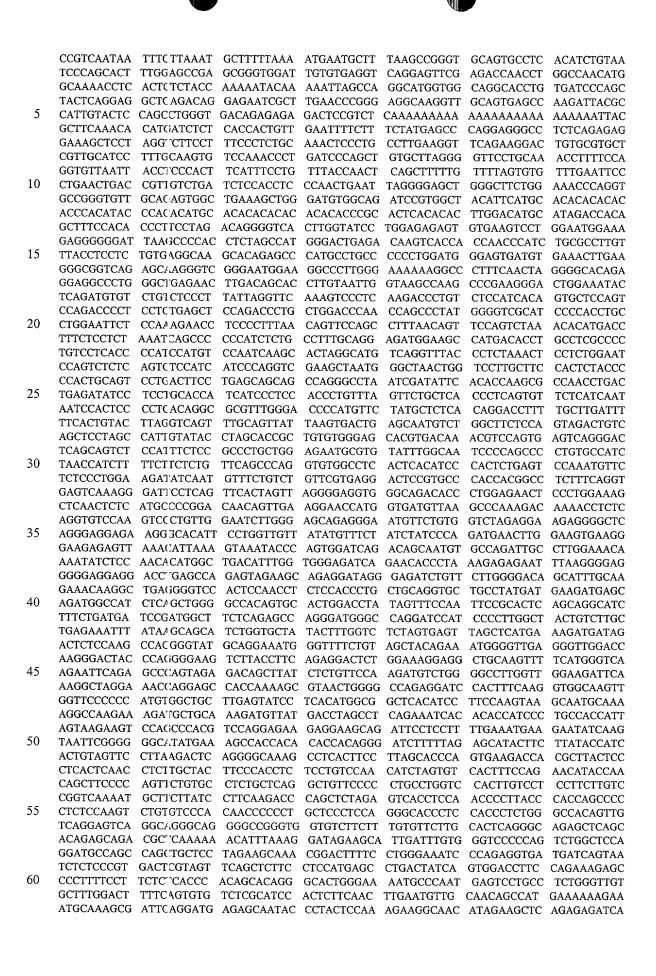
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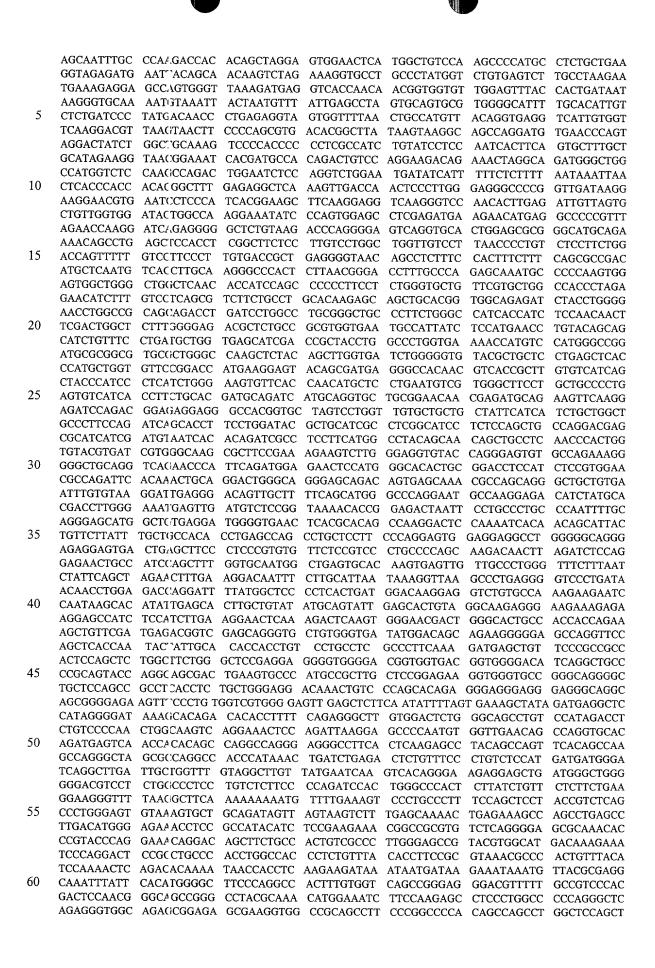
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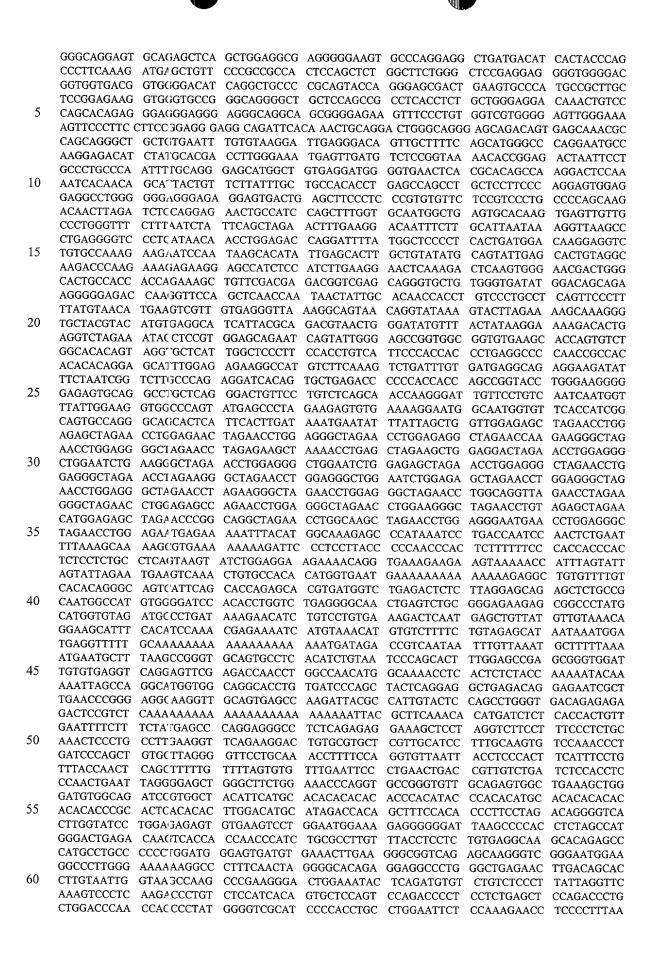
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  - 5'-GGGCGTCCGGGCCGTCGGG-3' (FRAG. NO:2273) (SEQ. ID NO:2286)
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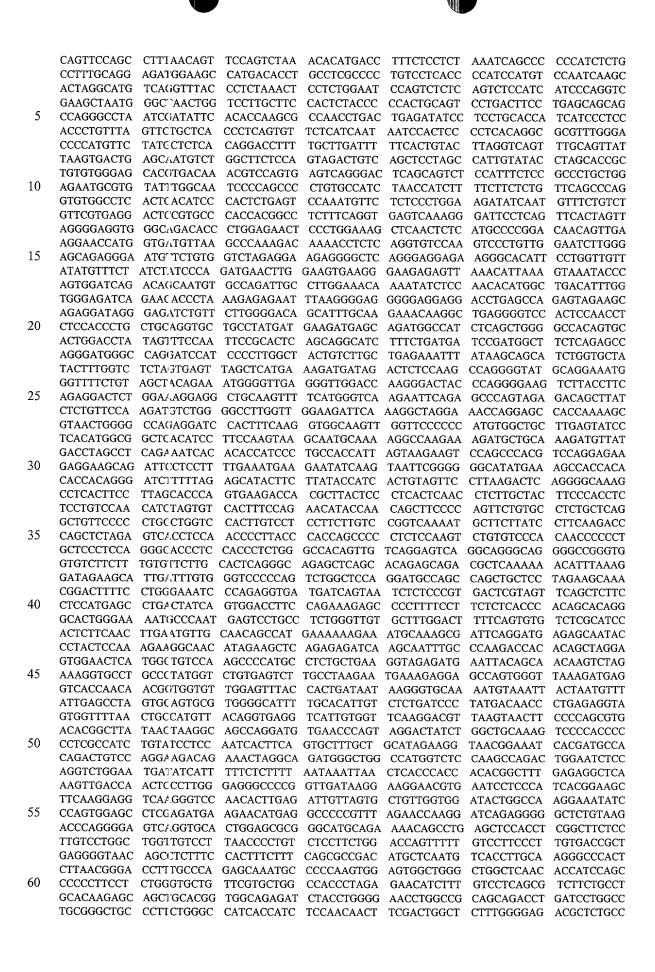
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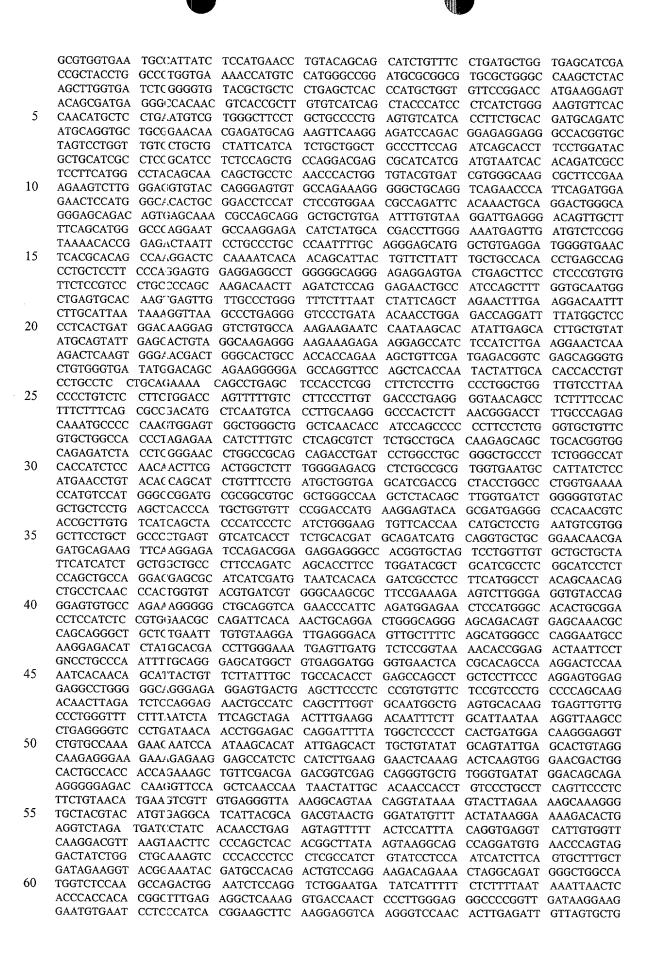
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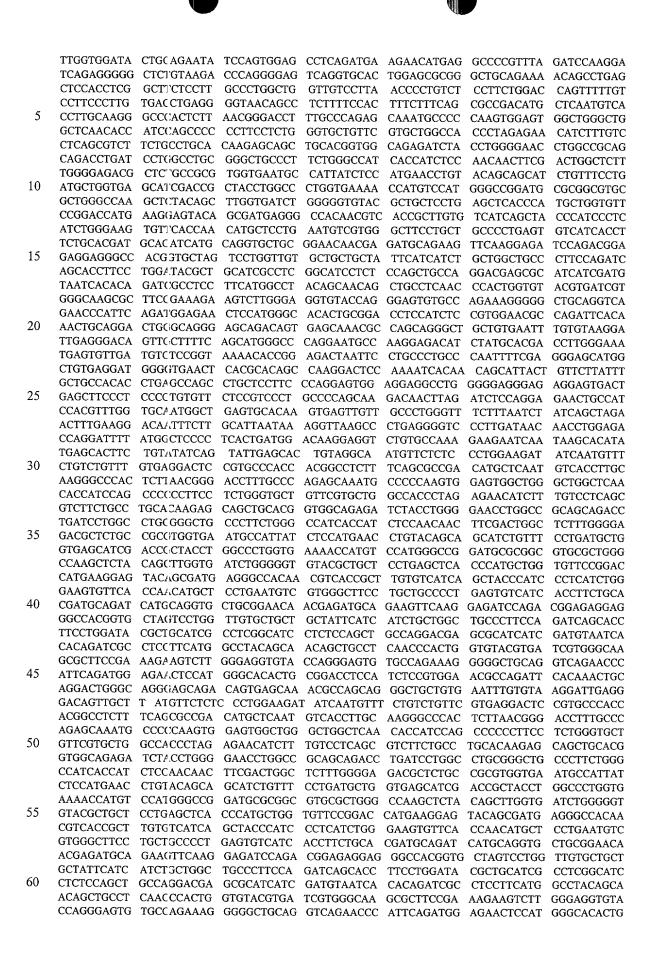


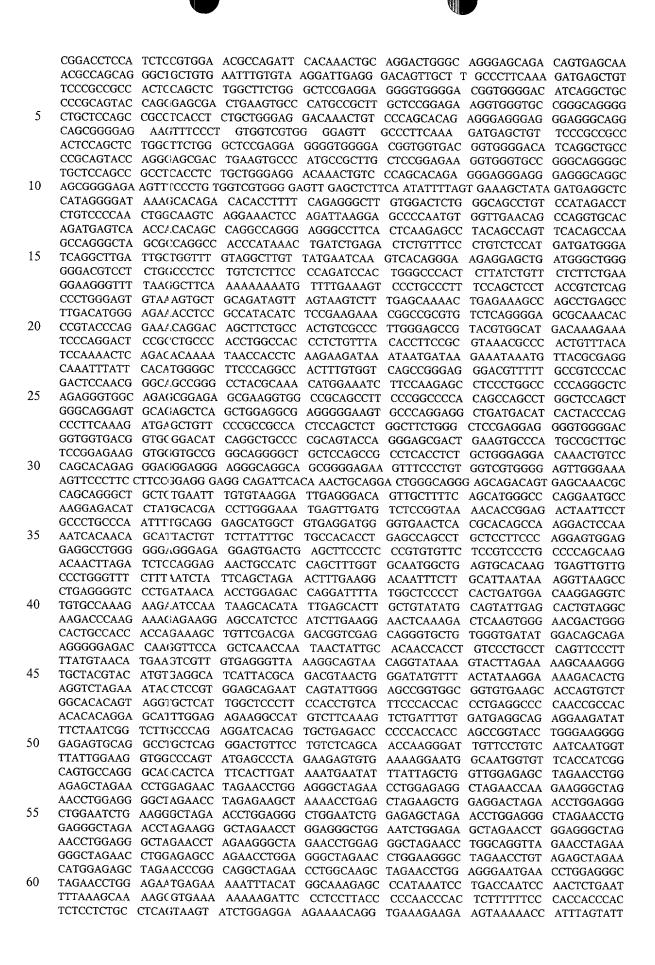


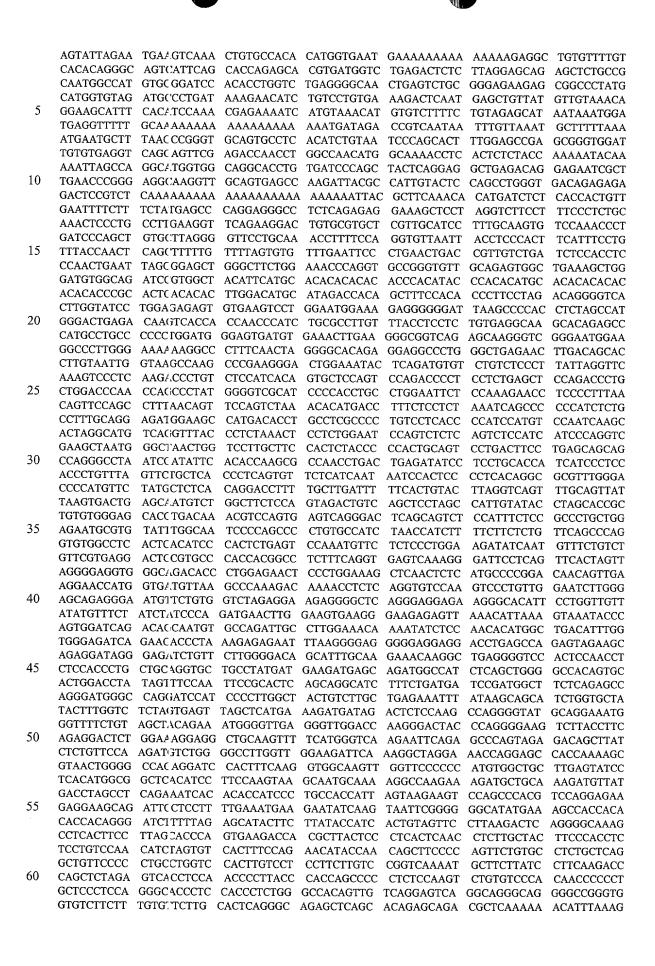


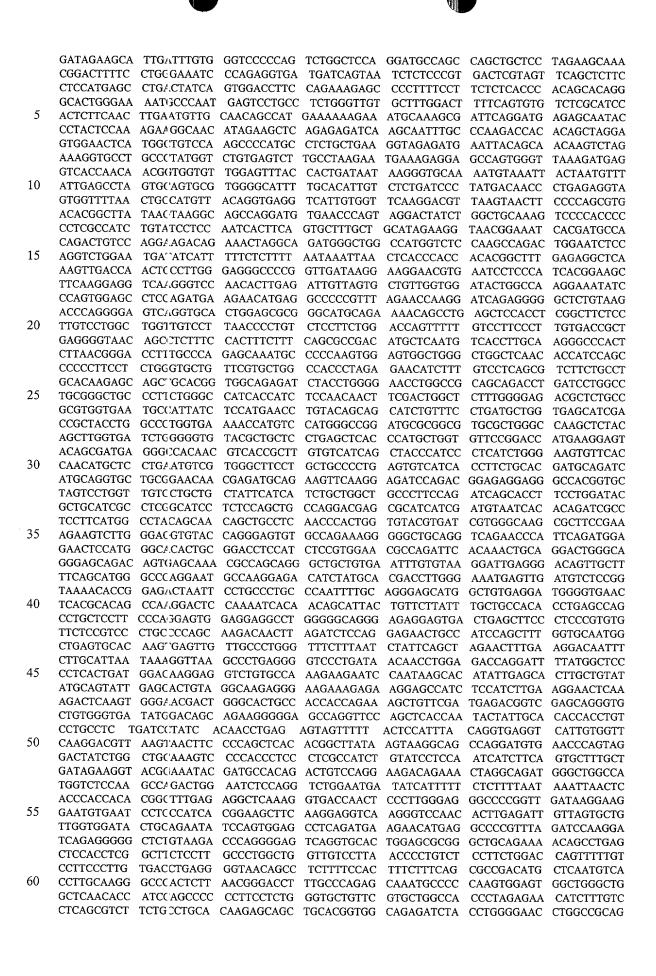


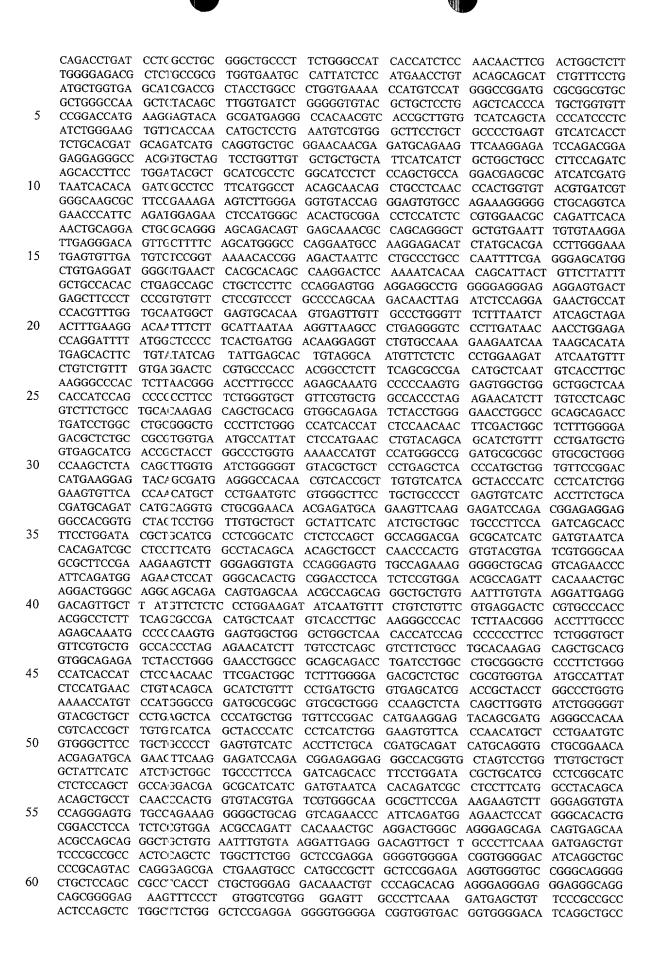












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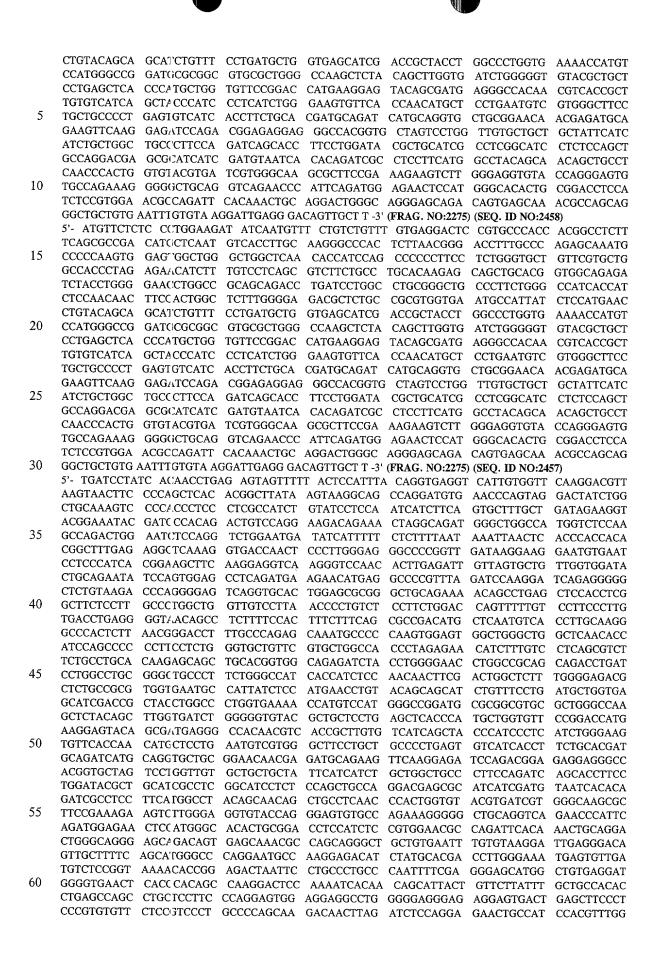


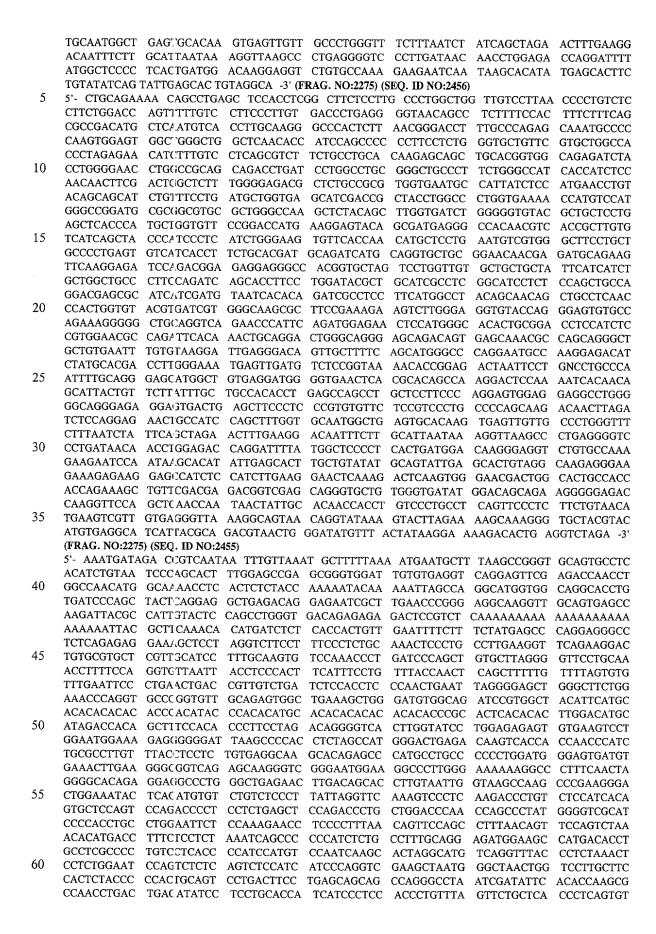
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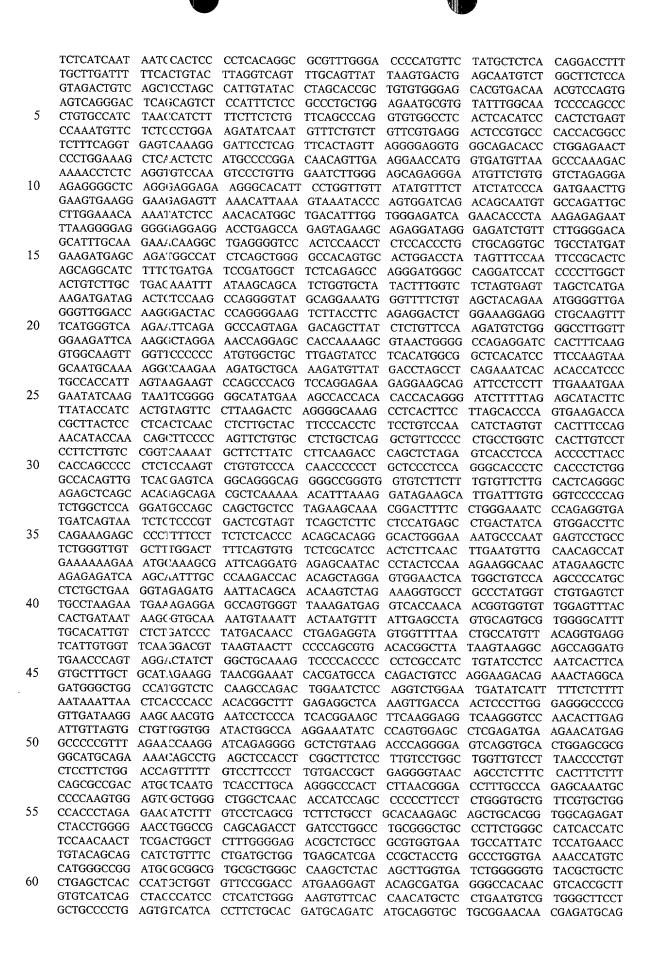
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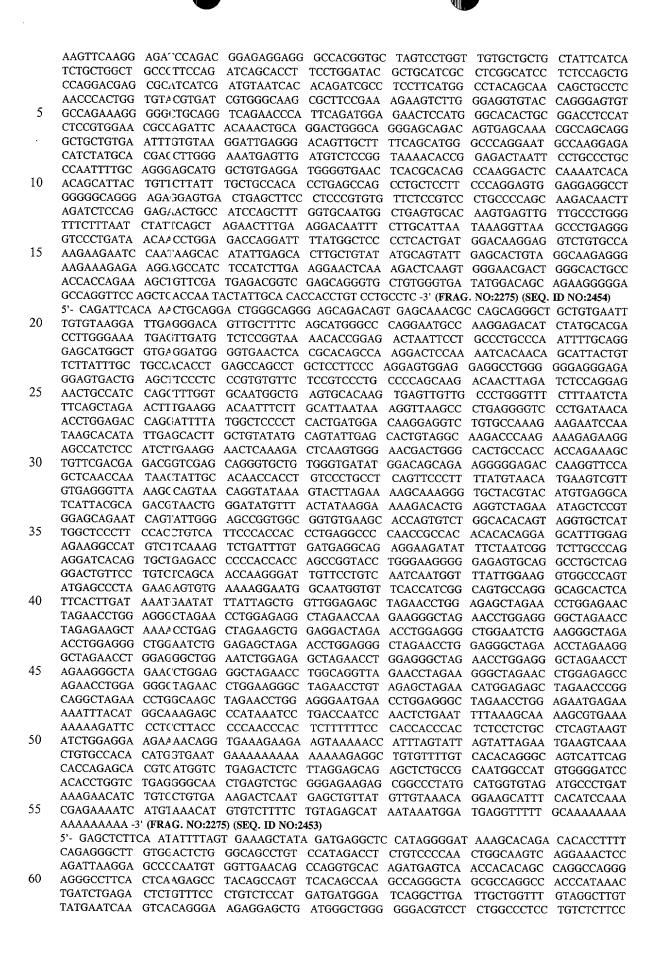
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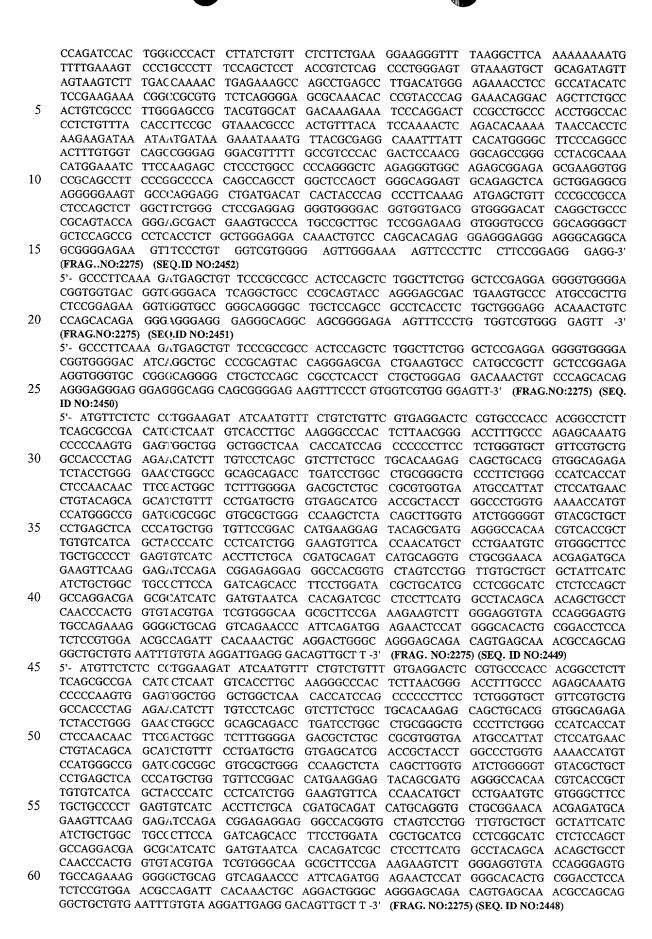
- 5'- ATGTTCTCTC CCTGGAAGAT ATCAATGTTT CTGTCTGTTC GTGAGGACTC CGTGCCCACC ACGGCCTCTT TCAGCGCCGA CATGCTCAAT GTCACCTTGC AAGGGCCCAC TCTTAACGGG ACCTTTGCCC AGAGCAAATG CCCCCCAAGTG GAGIGGCTGG GCTGGCTCAA CACCATCCAG CCCCCCTTCC TCTGGGTGCT GTTCGTGCTG GCCACCCTAG AGAA CATCTT TGTCCTCAGC GTCTTCTGCC TGCACAAGAG CAGCTGCACG GTGGCAGAGA TCTACCTGGG GAACCTGGCC GCAGCAGACC TGATCCTGGC CTGCGGGCTG CCCTTCTGGG CCATCACCAT CTCCAACAAC TTCGACTGGC TCTTTGGGGA GACGCTCTGC CGCGTGGTGA ATGCCATTAT CTCCATGAAC

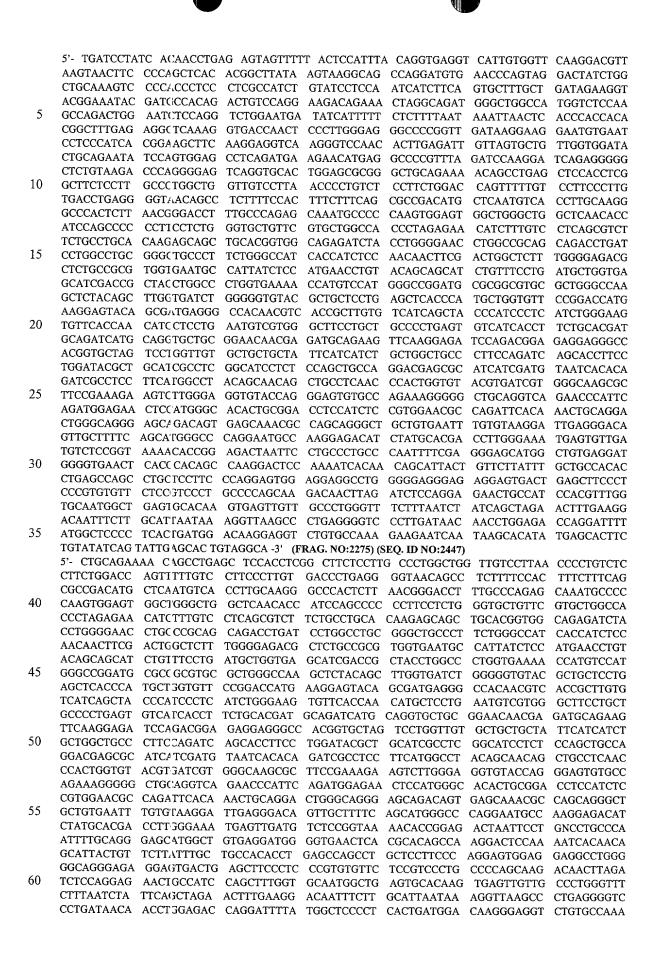


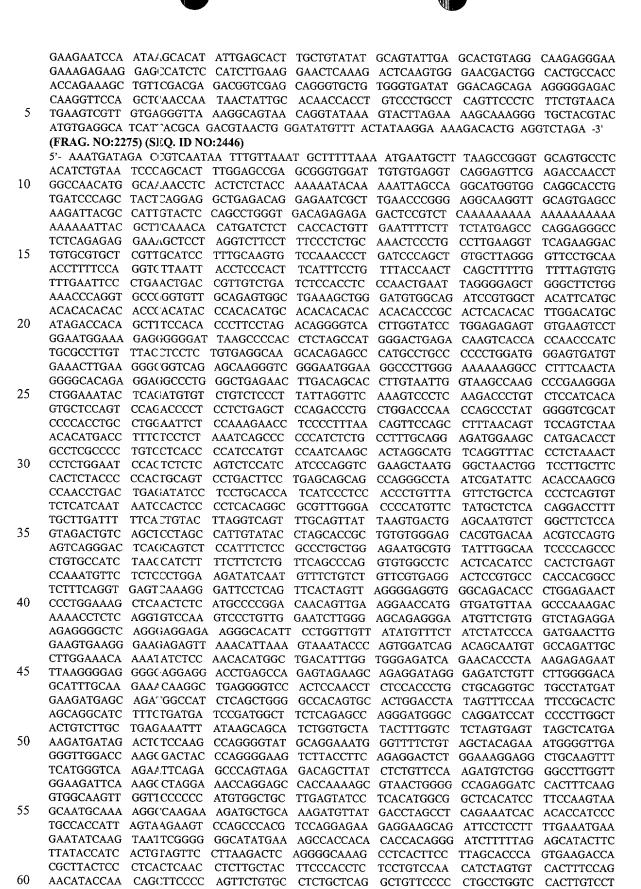






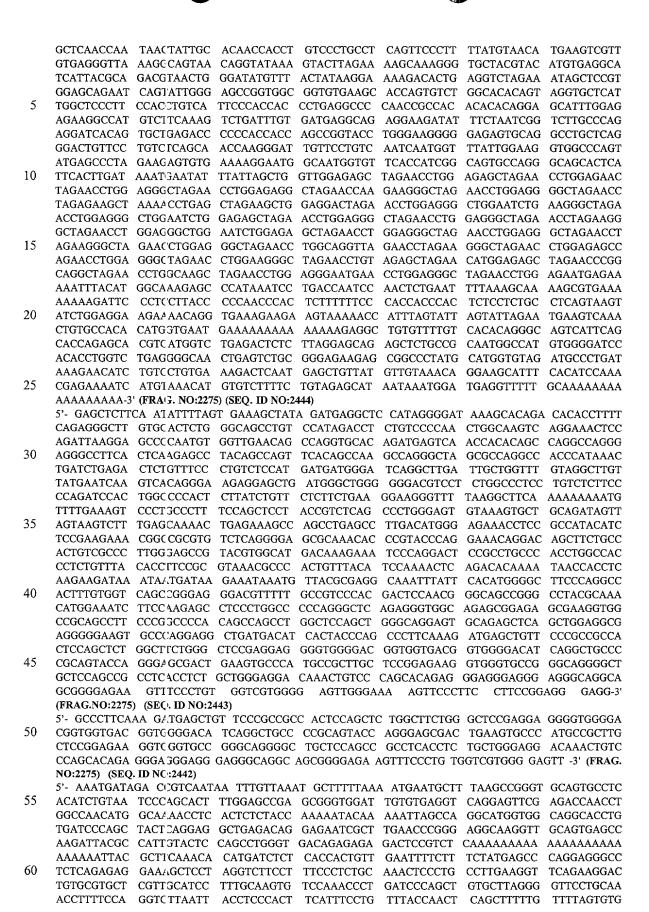


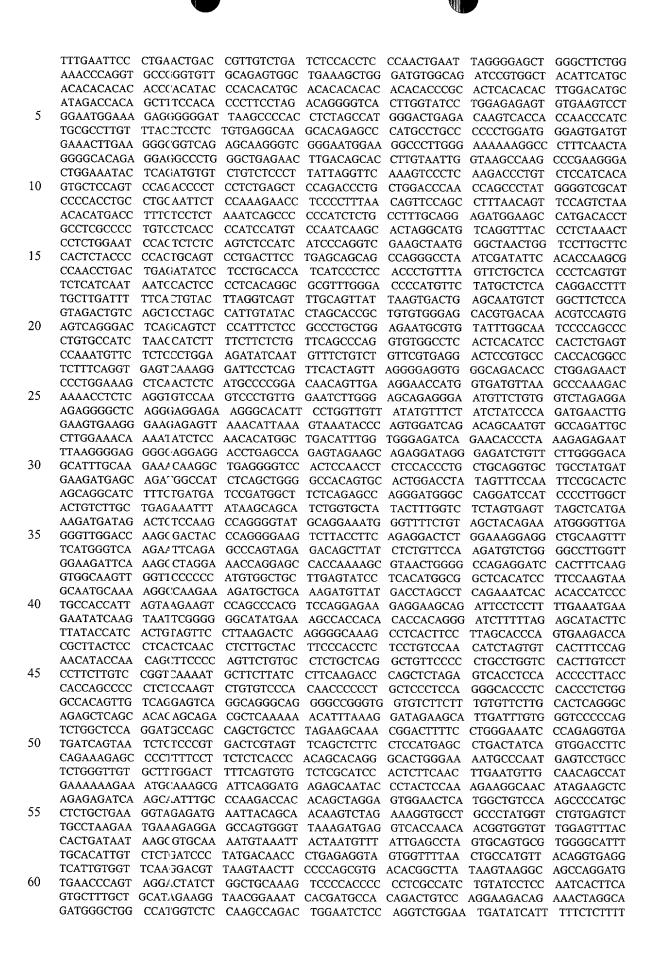


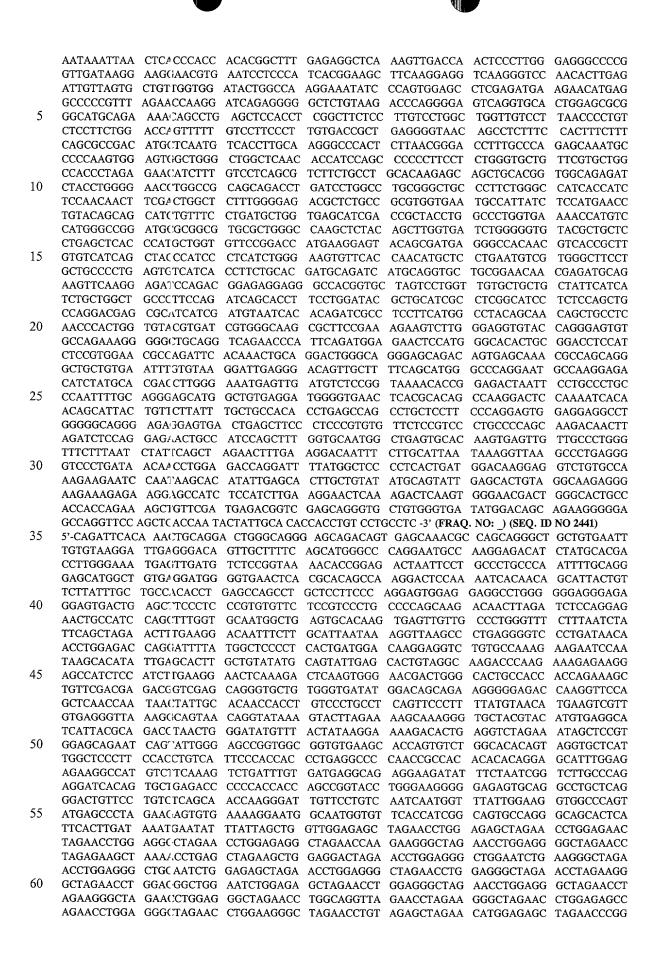


CCTTCTTGTC CGGTCAAAAT GCTTCTTATC CTTCAAGACC CAGCTCTAGA GTCACCTCCA ACCCCTTACC CACCAGCCCC CTCTCCAAGT CTGTGTCCCA CAACCCCCCT GCTCCCTCCA GGGCACCCTC CACCCTCTGG











5'-GGAGATAATGGCATTCACCACGCGGC-3' (FRAG. NO:2281) (SEQ. ID NO:2294)

5'-GGCCCAGCGCACGCCGCATCCGGCCC-3' (FRAG. NO:2282) (SEQ. ID NO:2295)

5'-GGGTTCTGACCTGC'AGCCCCC-3' (FRAG. NO:2283) (SEQ. ID NO:2296)

5'-GTCTCCTTGGCATTCCTGGGCCC-3' (FRAG. NO:2284) (SEQ. ID NO:2297)

5'-CAGTCACTCCTCCCTGCCCCC-3' (FRAG. NO:2285) (SEQ. ID NO:2298) 5'-CTTGCTGGGGCAGGGACGG-3' (FRAG. NO:2286) (SEQ. ID NO:2299)

5'-GGTGBCBTTGBGCETGTCGGCGC-3' (FRAG. NO:2287) (SEQ. ID NO:2300)

5'-GGTCCCGTTBBGBCTGGGCCC-3' (FRAG. NO:2288) (SEQ. ID NO:2301)

5'-GCCAGCCCACTCCACTTGGGGGC-3' (FRAG. NO:2289) (SEQ. ID NO:2302)

5'-GGGTGGCCAGCACGAACAGCACCCAGAGGAAGGGGGGC-3' (FRAG. NO:2290) (SEQ. ID NO:2303)

5'-GGCCCAGAAGGGC AGCCCGCAGGCCAGGATCAGGTCTGCTGCGGCC-3'(FRAG.NO:2291)(SEQ.ID NO:2304)

5'-GGAGATAATGGCATTCACCACGCGGC-3' (FRAG. NO:2292) (SEQ. ID NO:2305)

5'-GGCCCAGCGCACGCCGCGCATCCGGCCC-3' (FRAG. NO:2293) (SEQ. ID NO:2306)

5'-GGGTTCTGACCTGC AGCCCCC-3' (FRAG. NO:2294) (SEQ. ID NO:2307)

5'-GTCTCCTTGGCATTCCTGGGCCC-3' (FRAG. NO:2295) (SEQ. ID NO:2308)

5'-CAGTCACTCCTCTCCCTGCCCCC3' (FRAG. NO:2296) (SEQ. ID NO:2309)

5'-CTTGCTGGGGCAG(iGACGG-3' (FRAG. NO:2297) (SEQ. ID NO:2310)

5'-CCGTGTTGTCBGTGGTGCTG-3' (FRAG. NO:2298) (SEO. ID NO:2311) 5'-CCCGTTTGBGGTBTGGC-3' (FRAG. NO:2299) (SEQ. ID NO:2312)

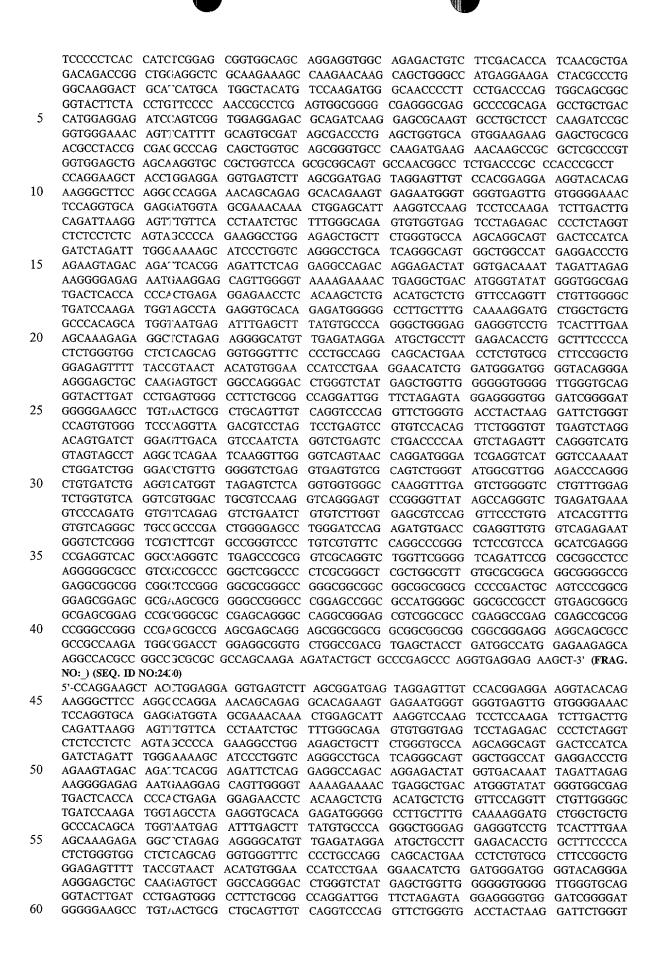
5'-GCTCCBCCBBTTCCCTTTTCTCC-3' (FRAG. NO:2300) (SEQ. ID NO:2313)

5'-TTGTTTTCCGTTTC~CTTG-3' (FRAG. NO:2301) (SEQ. ID NO:2314)

5'-CCGTCTGTGGTT-3' (FRAG. NO:2302) (SEQ. ID NO:2315)

#### **β2 Adrenergic Receptor Kinase Nucleic Acids and Antisense Oligonucleotide Fragments**

5'- GCCGCCGCCG CCAAGATGGC GGACCTGGAG GCGGTGCTGG CCGACGTGAG CTACCTGATG GCCATGGAGA 40 AGAGCAAGGC CACGCCGGCC GCGCGCCCA GCAAGAAGAT ACTGCTGCCC GAGCCCAGCA TCCGCAGTGT CATGCAGAAG TACCTGGAGG ACCGGGGCGA GGTGACCTTT GAGAAGATCT TTTCCCAGAA GCTGGGGTAC CTGCTCTTCC GAGACTTCTG CCTGAACCAC CTGGAGGAGG CCAGGCCCTT GGTGGAATTC TATGAGGAGA TCAAGAAGTA CGACAAGCTG GAGACGGAGG AGGAGCGTGT GGCCCGCAGC CGGGAGATCT TCGACTCATA CATCATGAAG GAGCTGCTGG CCTGCTCGCA TCCCTTCTCG AAGAGTGCCA CTGAGCATGT CCAAGGCCAC CTGGGGAAGA AGCAGGTGCC TCCGGATCTC TTCCAGCCAT ACATCGAAGA GATTTGTCAA AACCTCCGAG GGGACGTGTT CCACAAATTC ATTGAGAGCG ATAAGTTCAC ACGGTTTTGC CAGTGGAAGA ATGTGGAGCT CAACATCCAC CTGACCATGA ATGACTTCAG CGTGCATCGC ATCATTGGGC GCGGGGGCTT TGGCGAGGTC TATGGGTGCC GGAAGGCTGA CACAGGCAAG ATGTACGCCA TGAAGTGCCT GGACAAAAAG CGCATCAAGA TGAAGCAGGG GGAGACCTG GCCCTGAACG AGCGCATCAT GCTCTCGCTC GTCAGCACTG GGGACTGCCC 50 ATTCATTGTC TGCATGTCAT ACGCGTTCCA CACGCCAGAC AAGCTCAGCT TCATCCTGGA CCTCATGAAC GGTGGGGACC TGCACTACCA CCTCTCCCAG CACGGGGTCT TCTCAGAGGC TGACATGCGC TTCTATGCGG CCGAGATCAT CCTGGGCCTG GAGCACATGC ACAACCGCTT CGTGGTCTAC CGGGACCTGA AGCCAGCCAA CATCCTTCTG GACGAGCATG GCCACGTGCG GATCTCGGAC CTGGGCCTGG CCTGTGACTT CTCCAAGAAG AAGCCCCATG CCACCGTGGG CACCCACGGG TACATGGCTC CGGAGGTCCT GCAGAAGGGC GTGGCCTACG ACAGCAGTGC CGACTGGTTC TCTCTGGGGT GCATGCTCTT CAAGTTGCTG CGGGGGCACA GCCCCTTCCG GCAGCACAAG ACCAAAGACA AGCATGAGAT CGACCGCATG ACGCTGACGA TGGCCGTGGA GCTGCCCGAC TCCTTCTCCC CTGAACTACG CTCCCTGCTG GAGGGGTTGC TGCAGAGGGA TGTCAACCGG AGATTGGGCT GCCTGGGCCG AGGGGCTCAG GAGGTGAAAG AGAGCCCCTT TTTCCGCTCC CTGGACTGGC AGATGGTCTT CTTGCAGAAG TACCCTCCCC CGCTGATCCC CCCACGAGGG GAGGTGAACG CGGCCGACGC CTTCGACATT GGCTCCTTCG ATGAGGAGGA CACAAAAGGA ATCAAGTTAC TGGACAGTGA TCAGGAGCTC TACCGCAACT





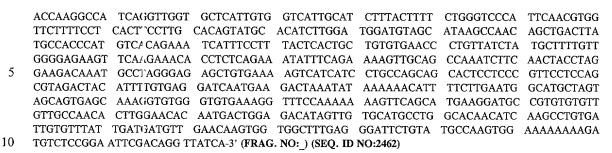
GCCTGGGCCG AGGGGCTCAG GAGGTGAAAG AGAGCCCCTT TTTCCGCTCC CTGGACTGGC AGATGGTCTT CTTGCAGAAG TACCCTCCC CGCTGATCCC CCCACGAGGG GAGGTGAACG CGGCCGACGC CTTCGACATT GGCCTCTCG ATGAGGAGGA CACAAAAGGA ATCAAGTTAC TGGACAGTGA TCAGGAGCTC TACCGCAACT TCCCCCTCAC CATCTCGGAG CGGTGGCAGC AGGAGGTGGC AGAGACTGTC TTCGACACCA TCAACGCTGA GACAGACCGG CTGCAGGCTC GCAAGAAAGC CAAGAACAAG CAGCTGGGCC ATGAGGAAGA CTACGCCCTG GGCAAGGACT GCATCATGCA TGGCTACATG TCCAAGATGG GCAACCCCTT CCTGACCCAG TGGCAGCGCG GGTACTTCTA CCTGTTCCCC AACCGCCTCG AGTGGCGGGG CGAGGGCGAG GCCCCGCAGA GCCTGCTGAC CATGGAGAAC AGTTCATTT GCAGTGCAG AGCGCAACT AGCGCCTG AGCTGCTGCC GGTGGGAAAC AGTTCATTTT GCAGTGCGAT AGCGACCCTT AGCTGGTGCA GTGGAAGAAG GAGCTGCCCG ACGCCTACCG CGAC GCCCAG CAGCTGGTCC CAAGATCAAG AACAAGCCGC GCTCGCCCGT GGTGGAGCTG AGCAAGGTGC CGCTGGTCCA GCCGGCGAGT GCCAACGGCC TCTGACCCCGC GCTCGCCCGT GGTGGAGCTG AGCAAGGTGC CGCTGGTCCA GCCGGCAGT GCCAACGGCC TCTGACCCCC CCACCCGCCT-3' (FRAG. NO:\_) (SEQ. II) NO:2428)

## 50 CCR-2 CC Chemoltine Receptor Nucleic Acids and Antisense Oligonucleotide Fragments

5'-CTTTGTGAAG AAGGAATTGG CAACACTGAA ACCTCCAGAA CAAAGGCTGT CACTAAGGTC CCGCTGCCTT
GATGGATTAT ACAC'TTGACC TCAGTGTGAC AACAGTGACC GACTACTACT ACCCTGATAT CTTCTCAAGC
CCCTGTGATG CGGAACTTAT TCAGACAAAT GGCAAGTTGC TCCTTGCTGT CTTTTATTGC CTCCTGTTTG
TATTCAGTCT TCTG-3GAAAC AGCCTGGTCA TCCTGGTCCT TGTGGTCTGC AAGAAGCTGA GGAGCATCAC

55 AGATGTATAC CTC'TTGAACC TGGCCCTGTC TGACCTGCTT TTTGTCTTCT CCTTCCCCTT TCAGACCTAC
TATCTGCTGG ACCAGTGGGT GTTTGGGACT GTAATGTGCA AAGTGGTGTC TGGCTTTTAT TACATTGGCT
TCTACAGCAG CATC'TTTTC ATCACCCTCA TGAGTGTGGA CAGGTACCTG GCTGTTGTCC ATGCCGTGTA
TGCCCTAAAG GTGAGGACGA TCAGGATGGG CACAACGCTG TGCCTGGCAG TATGGCTAAC CGCCATTATG
GCTACCATCC CATTGCTAGT GTTTTACCAA GTGGCCTCTG AAGATGGTGT TCTACAGTGT TATTCATTTT

60 ACAATCAACA GAC'TTGAAG TGGAAGATCT TCACCAACTT CAAAATGAAC ATTTTAGGCT TGTTGATCCC
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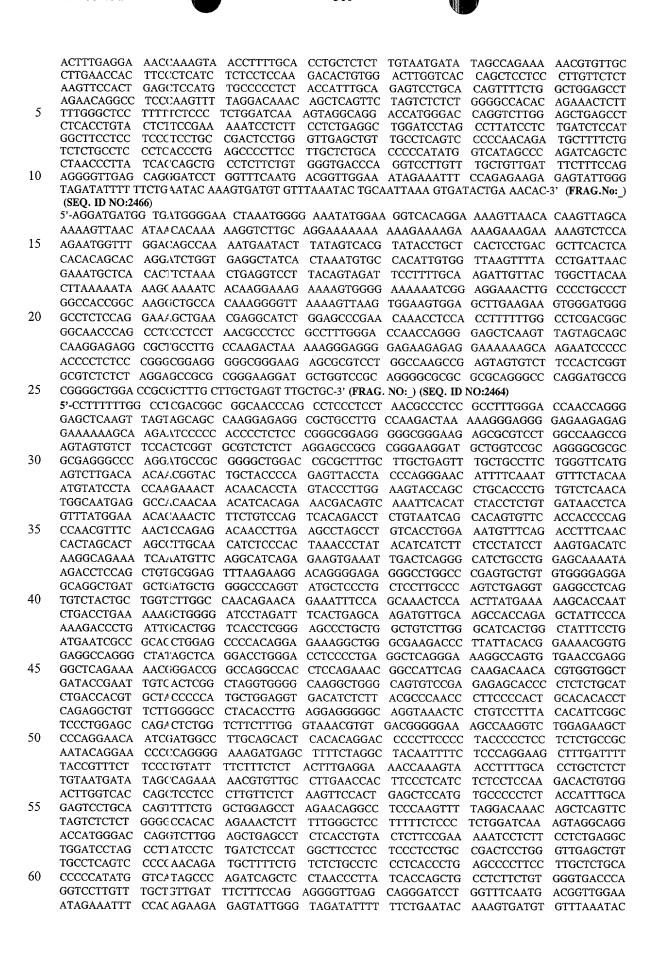
### CCR-4 CC Chemoline Receptor Nucleic Acids and Antisense Oligonucleotide Fragments

5'-TTTCATCTCT CCCGGCTTAT TTGCTGGTTT CTCCGAATGC GGGCCTTGTC TGGTTCACGC TGGATCCCCA ACGCCTAGAA CAGTGCGTGG CACGCAGTTC GTCCTTCTAT AAATATCGGA CTAAATGCAT CTCTGTGATG GTAATACCCA CACCGTGTTG TGAGAATGAA TGAGTGATTC TGTGCAAGTT CCTAGTGATC TGTTACAAAA AGTACTGGTC GCTAAATTAC TCTTATAATA AAGCATACTT TTAGGATAAT AAAGCACTAT TCGCGAATTG GTTACCGCTA TTATGAAATT ACTGAGCAAT ACATATCTAC ATCTGATCAG TCTCCAGAAT TATGCCAAAT CCTACCTTCT TCTGAAAGTA TCTCCTAATT ATCTGCACCT GACCCTAGTG ATGCTGTGAA TGTGCAAGTA TAGCTACATC CTCCGAAGGA AGGATCTTTA CTCCTTTTAC CTCCTGAATG GGCTGCGTCT GCTGAAAGCG CGGGGGAATG GGCGGTTGGA AGCTTGGCCC TACTTCCAGC ATTGCCGCCT ACTGGTTGGG TTACTCCAGC AAGTCACTCC CCTTCCCTGG GCCTCAGTGT CTCTACTGTA GCATTCCCAG GTCTGGAATT CCATCCACTT TAGCAAGGAT GGACGCCCA CAGAGAGACG CGTTCCTAGC CCGCGCTTCC CACCTGTCTT CAGGCGCATC CCGCTTCCCT CAAACTTAGG AAATGCCTCT GGGAGGTCCT GTCCGGCTCC GGACTCACTA CCGACCACCC GCAAACAGCA GGG\*CCCCTG GGCTTCCCAA GCCGCGCACC TCTCCGCCCC GCCCCTGCGC CCTCCTTCCT CGCGTCTGCC CCTCTCCCC ACCCCGCCTT CTCCCTCCCC GCCCCAGCGG CGCATGCGCC GCGCTCGGAG CGTGTTTTTA TAAAAGTCCG GCCGCGCCA GAAACTTCAG TTTGTTGGCT GCGGCAGCAG GTAGCAAAGT GACGCCGAGG GCCTGAGTGC TCCAGTAGCC ACCGCATCTG GAGAACCAGC GGTTACCATG GAGGGGATCA GTGTAAGTCC AGTTTCAACC TGCTTTGTCA TAAATGTACA AACGTTTGAA CTTAGAGCGC AGCCCCTCTC CGAGCGGCA GAAGCGGCCA GGACATTGGA GGTACCCGTA CTCCAAAAAA GGGTCACCGA AAGGAGTTTT CTTGACCATG CCTATATAGT GCGGGTGGGT GGGGGGGGGA CAGGATTGGA ATCTTTTTCT CTGTGAGTCG AGGAGAAACG ACTGGAAAGA GCGTTCCAGT GGCTGCATGT GTCTCCCCCT TGAGTCCCGC CGCGCGGGC GGCTTGCACG CTGTTTGCAA ACGTAAGAAC ATTCTGTGCA CAAGTGCAGA GAAGGCGTGC GCGCTGCCTC GGGACTCAGA CCACCGGTCT CTTCCTTGGG GAAGCGGGGA TGTCTTGGAG CGAGTTACAT TGTCTGAATT TAGAGGCGGA GGGCGCGTG CCTGGGCTGA CTTCCCAGGA GGAGATTGCG CCCGCTTTAA CTTCGGGGTT AAGCGCCTGG TGACTGTTCT TGACACTGGG TGCGTGTTTG TTAAACTCTG TGCGGCCGAC GGAGCTGTGC CAGTCTCCCA GCACAGTAGG CAGAGGGCGG GAGAGGCGGG TGGACCCACC GCGCCGATCC TCTGAGGGGA TCGAGTGGTG GCAC CAGCTA GGAGTTGATC CGCCCGCGCG CTTTGGGTTT GAGGGGGAAA CCTTCCCGCC GTCCGAAGCG CGCCTCTTCC CCACGGCCGC GAGTGGGTCC TGCAGTTCGA GAGTTTGGGG TCGTGCAGAG GTCAGCGGAG TGGTTTGACC TCCCCTTTGA CACCGCGCAG CTGCCAGCCC TGAGATTTGC GCTCCGGGGA TAGGAGCGGG TACCGGGTGA GGGGCGGGGG CGGTTAAGAC CGCACCTGGG CTGCCAGGTC GCCGCCGCA AGACTGGCAG GTGCAAGTGG GGAAACCGTT TGGCTCTCTC CGAGTCCAGT TGTGATGTTT AACCGTCGGT GGTTTCCAGA AACCTTTTGA AACCCTCTTG CTAGGGAGTT TTTGGTTTCC TGCAGCGGCG CGCAATTCAA AGACGCTCGC GGCCGAGCCG CCCAGTCGCT CCCCAGCACC CTGTGGGACA GAGCCTGGCG TGTCGCCCAG CGGAGCCCCT GCACCGCTGC TTGCGGGCGG TTGGCGTGGG TGTAGTGGGC AGCCGCGGCG GCCCGGGGCT GGACGACCCG GCCCCCGCG TGCCCACCGC CTGGAGGCTT CCAGCTGCCC ACCTCCGGCC GGGTTAACTG GATCAGTGGC GGGGTAATGG GAAGCCACCC GGGAGAGTGA GGAAATGAAA CTTGGGGCGA GGACCACGGG TGCAGACCCC GTTACCTTCT CCACCCAGGA AAATGCCCCG CTCCCTAACG TCCCAAACGC GCCAAGTGAT AAACACGAGG ATGCCAAGAG ACCCACACAC CGGAGGAGGAGCG CCCGCTTGGG GGAGGAGGTG CCGTTTGTTC ATTTTCTGAC ACTCCCGCCC AATATACCCC AAGCACCGAA GGGCCTTCGT TTTAAGACCG CATTCTCTTT ACCCACTACA AGTIGCTTGA AGCCCAGAAT GGTTTGTATT TAGGCAGGCG TGGGAAAATT AAGTTTTTGC GCTTTAGGAG AAT(AGTCTT TGCAACGCCC CCGCCCTCCC CCCGTGATCC TCCCTTCTCC CCTCTTCCCT CCCTGGGCGA AAAACTTCTT ACAAAAAGTT AATCACTGCC CCTCCTAGCA GCACCCACCC CACCCCCAC GCCGCCTGGG AGTGGCCTCT TTGTGTGTAT TTTTTTTTC CTCCTAAGGA AGGTTTTTTT TCTTCCCTCT AGTGGGCGGG GCAGAGGAGT TAGCCAAGAT GTGACTTTGA AACCCTCAGC GTCTCAGTGC CCTTTTGTTC TAAACAAAGA ATTITGTAAT TGGTTCTACC AAAGAAGGAT ATAATGAAGT CACTATGGGA AAAGATGGGG AGGAGAGTTG TAGGATTCTA CATTAATTCT CTTGTGCCCT TAGCCCACTA CTTCAGAATT TCCTGAAGAA AGCAAGCCTG AAT. GGTTTT TTAAATTGCT TTAAAAATTT TTTTTAACTG GGTTAATGCT TGCTGAATTG GAAGTGAATG TCC/.TTCCTT TGCCTCTTTT GCAGATATAC ACTTCAGATA ACTACACCGA GGAAATGGGC TCAGGGGACT ATGACTCCAT GAAGGAACCC TGTTTCCGTG AAGAAAATGC TAATTTCAAT AAAATCTTCC TGCCCACCAT CTACTCCATC ATCTTCTTAA CTGGCATTGT GGGCAATGGA TTGGTCATCC TGGTCATGGG TTACCAGAAG AAACTGAGAA GCATGACGGA CAAGTACAGG CTGCACCTGT CAGTGGCCGA CCTCCTCTTT GTCATCACGC TTCCCTTCTG GGCAGTTGAT GCCGTGGCAA ACTGGTACTT TGGGAACTTC CTATGCAAGG



# 25 CD-34 Nucleic Acics and Antisense Oligonucleotide Fragments

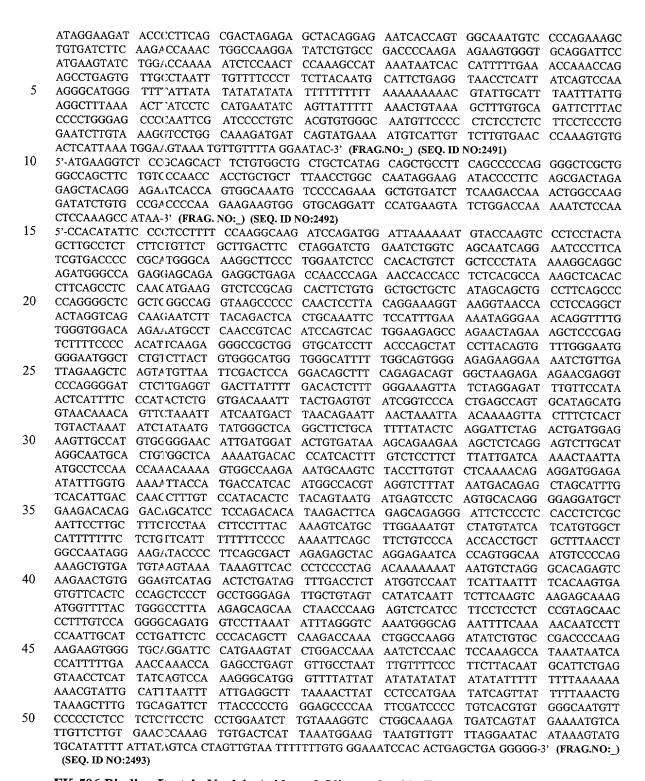
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CACACAGCAC AGGATCTGGT GAGGCTATCA TAAATGTGC CACATTGTGG TTAAGTTTTA CCTGATTAAC
GAAATGCTCA CACTTCTAAA CTGAGGTCCT TACAGTAGAT TCCTTTTGCA AGATTGTTAC TGGCTTACAA CTTAAAAATA AAGCAAAATC ACAAGGAAAG AAAAGTGGGG AAAAAATCGG AGGAAACTTG CCCCTGCCCT GGCCACCGGC AAGCCTGCA CAAAGGGGTT AAAAGTTAAG TGGAAGTGGA GCTTGAAGAA GTGGGATGGG GCCTCTCCAG GAAAGCTGAA CGAGGCATCT GGAGCCCGAA CAAACCTCCA CCTTTTTTGG CCTCGACGGC GGCAACCCAG CCTCCCTCCT AACGCCCTCC GCCTTTGGGA CCAACCAGGG GAGCTCAAGT TAGTAGCAGC CAAGGAGAGG CGCTGCCTTG CCAAGACTAA AAAGGGAGGG GAGAAGAGG GAAAAAAGCA AGAATCCCCC ACCCCTCTCC CGGGCGGAGG GGGCGGGAAG AGCGCGTCCT GGCCAAGCCG AGTAGTGTCT TCCACTCGGT GCGTCTCTCT AGGAGCCGCG CGGGAAGGAT GCTGGTCCGC AGGGGCGCGC GCGCAGGGCC CAGGATGCCG CGGGGCTGGA CCGCGCTTTG CTTGCTGAGT TTGCTGC CCTTTTTTGG CCTCGACGGC GGCAACCCAG CCTCCCTCCT AACGCCCTCC GCCTTTGGGA CCAACCAGGG GAGCTCAAGT TAGTAGCAGC CAAGGAGAGG CGCTGCCTTG CCAAGACTAA AAAGGGAGGG GAGAAGAGAG GAAAAAAGCA AGAATCCCCC ACCCCTCTCC CGGGCGGAGG GGGCGGAAG AGCGCGTCCT GGCCAAGCCG AGTAGTGTCT TCCACTCGGT GCGTCTCTCT AGGAGCCGCG CGGCIAAGGAT GCTGGTCCGC AGGGGCGCGC GCGAGGGCCC AGGATGCCGC GGGGCTGGAC CGCGCTTTGC TTGCTGAGTT TGCTGCCTTC TGGGTTCACA ACTACTCTA CCCAAGAAACT ACAACACCTA GTACCCTTGG AAGTACCAGC CTGCACCCTG TGTCTCAACA TGGCAATGAG GCCACAACAA ACATCACAGA AACGACAGTC AAA: TCACAT CTACCTCTGT GATAACCTCA GTTTATGGAA ACACAAACTC TTCTGTCCAG 50 ACAGGGGAGA GGGCCTGGCC CGAGTGCTGT GTGGGGAGGA GCAGGCTGAT GCTGATGCTG GGGCCCAGGT ATGCTCCCTG CTCCITGCCC AGTCTGAGGT GAGGCCTCAG TGTCTACTGC TGGTCTTGGC CAACAGAACA GAAATTTCCA GCAAACTCCA ACTTATGAAA AAGCACCAAT CTGACCTGAA AAAGCTGGGG ATCCTAGATT TCACTGAGCA AGAIGTTGCA AGCCACCAGA GCTATTCCCA AAAGACCCTG ATTGCACTGG TCACCTCGGG AGCCCTGCTG GCTGTCTTGG GCATCACTGG CTATTTCCTG ATGAATCGCC GCAGCTGGAG CCCCACAGGA GAAAGGCTGG GCGAAGACCC TTATTACACG GAAAACGGTG GAGGCCAGGG CTATAGCTCA GGACCTGGGA CCTCCCCTGA GGCTCAGGGA AAGGCCAGTG TGAACCGAGG GGCTCAGAAA AACGGGACCG GCCAGGCCAC CTCCAGAAAC GGCCATTCAG CAAGACAACA CGTGGTGGCT GATACCGAAT TGTGACTCGG CTAGGTGGGG CAAGGCTGGG CAGTGTCCGA GAGAGCACCC CTCTCTGCAT CTGACCACGT GCTACCCCCA TGCTGGAGGT GACATCTCTT ACGCCCAACC CTTCCCCACT GCACACACCT CAGAGGCTGT TCTTGGGGCC CTACACCTTG AGGAGGGGC AGGTAAACTC CTGTCCTTTA CACATTCGGC TCCTGGAGC CAGACTCTGG TCTTCTTTGG GTAAACGTGT GACGGGGAA AGCCAAGGTC TGGAGAAGCT CCCAGGAACA ATCGATGGCC TTGCAGCACT CACACAGGAC CCCCTTCCCC TACCCCCTCC TCTCTGCCGC AATACAGGAA CCCCCAGGGG AAAGATGAGC TTTTCTAGGC TACAATTTC TCCCAGGAAG CTTTGATTTT TACCGTTTCT TCCCTGTATT TTCTTTCTCT





## **Eotaxin Antisense Nucleic Acids and Oligonucleotide Fragments**

5'-GCATTTTTC AAGTTTTATG ATTTATTTAA CTTGTGGAAC AAAAATAAAC CAGAAACCAC CACCTCTCAC GCCAAAGCTC ACACCTTCAG CCTCCAACAT GAAGGTCTCC GCAGCACTTC TGTGGCTGCT GCTCATAGCA GCTGCCTTCA GCCCCCAGGG GCTCGCTGGG CCAGCTTCTG TCCCAACCAC CTGCTGCTTT AACCTGGCCA ATAGGAAGAT ACCCCTTCAG CGACTAGAGA GCTACAGGAG AATCACCAGT GGCAAATGTC CCCAGAAAGC TGTGATCTTC AAGACCAAAC TGGCCAAGGA TATCTGTGCC GACCCCAAGA AGAAGTGGGT GCAGGATTCC ATGAAGTATC TGGA.CCAAAA ATCTCCAACT CCAAAGCCAT AAATAATCAC CATTTTTGAA ACCAAACCAG AGGCTTTAAA ACTTATCCTC CATGAATATC AGTTATTTTT AAACTGTAAA GCTTTGTGCA GATTCTTTAC GAATCTTGTA AAGCTCCTGG CAAAGATGAT CAGTATGAAA ATGTCATTGT TCTTGTGAAC CCAAAGTGTG ACTCATTAAA TGGAAGTAAA TGTTGTTTTA GGAATAC ATGAAGGTCT CCGCAGCACT TCTGTGGCTG CTGCTCATAG CAGCTGCCTT CAGCCCCCAG GGGCTCGCTG GGCCAGCTTC TGTCCCAACC ACCTGCTGCT TTAACCTGGC CAATAGGAAG ATACCCCTTC AGCGACTAGA GAGCTACAGG AGAATCACCA GTGGCAAATG TCCCCAGAAA GCTCTGATCT TCAAGACCAA ACTGGCCAAG GATATCTGTG CCGACCCCAA GAAGAAGTGG GTGCAGGATT CCATGAAGTA TCTGGACCAA AAATCTCCAA CTCCAAAGCC ATAA CCACATATTC CCCTCCTTTT CCAAGGCAAG ATCCAGATGG ATTAAAAAAT GTACCAAGTC CCTCCTACTA GCTTGCCTCT CTTCTGTTCT GCTTGACTTC CTAGGATCTG GAATCTGGTC AGCAATCAGG AATCCCTTCA TCGTGACCCC CGCATGGGCA AAGGCTTCCC TGGAATCTCC CACACTGTCT GCTCCCTATA AAAGGCAGGC AGATGGGCCA GAGGAGCAGA GAGGCTGAGA CCAACCCAGA AACCACCACC TCTCACGCCA AAGCTCACAC CTTCAGCCTC CAACATGAAG GTCTCCGCAG CACITCTGTG GCTGCTCC ATAGCAGCTG CCTTCAGCCC CCAGGGGCTC GCTGGGCCAG
GTAAGCCCCC CAACTCCTTA CAGGAAAGGT AAGGTAACCA CCTCCAGGCT ACTAGGTCAG CAAGAATCTT
TACAGACTCA CTGCAAATTC TCCATTTGAA AAATAGGGAA ACAGGTTTTG TGGGTGGACA AGAAATGCCT
CAACCGTCAC ATCCAGTCAC TGGAAGAGCC AGAACTAGAA AGCTCCCGAG TCTTTTCCCC ACATTCAAGA
GGGCCGCTGG GTGCATCCTT ACCCAGCTAT CCTTACAGTG TTTGGGAATG GGGAATGGCT CTGTCTTACT
GTGGGCATGG TGGCCATTTT TGGCAGTGGG AGAGAAGGAA AATCTGTTGA TTAGAAGCTC AGTATGTTAA TTCGACTCCA GGACAGCTTT CAGAGACAGT GGCTAAGAGA AGAACGAGGT CCCAGGGGAT CTCTTGAGGT GACTTATTTT GACACTCTTT GGGAAAGTTA TCTAGGAGAT TTGTTCCATA ACTCATTTTC CCATACTCTG GTGACAAATT TACIGAGTGT ATCGGTCCCA CTGAGCCAGT GCATAGCATG GTAACAAACA GTTCTAAATT ATCAATGACT TAAC'AGAATT AACTAAATTA ACAAAAGTTA CTTTCTCACT TGTACTAAAT ATCTATAATG TATGGGCTCA GGCTTCTGCA TTTTATACTC AGGATTCTAG ACTGATGGAG AAGTTGCCAT GTGGGGGAAC ATTGATGGAT ACTGTGATAA AGCAGAAGAA AGCTCTCAGG AGTCTTGCAT AGGCAATGCA CTGTGGCTCA AAAATGACAC CCA CACTTT GTCTCCTTCT TTATTGATCA AAACTAATTA ATGCCTCCAA CCAAACAAAA GTGGCCAAGA AATGCAAGTC TACCTTGTGT CTCAAAACAG AGGATGGAGA ATATTTGGTG AAAATTACCA TGACCATCAC ATGCCCACGT AGGTCTTTAT AATGACAGAG CTAGCATTTG TCACATTGAC CAAGCTTTGT CCATACACTC TACAGTAATG ATGAGTCCTC AGTGCACAGG GGAGGATGCT GAAGACACAG GACAGCATCC TCCAGACACA TAAGACTTCA GAGCAGAGGG ATTCTCCCTC CACCTCTCGC AATTCCTTGC TTTCTCCTAA CTTCCTTTAC AAACTCATGC TTGGAAATGT CTATGTATCA TCATGTGGCT CATTTTTTC TCTGTTCATT TTTTTTCCCC AAAATTCAGC TTCTGTCCCA ACCACCTGCT GCTTTAACCT GGCCAATAGG AAGATACCCC TTCAGCGACT AGAGAGCTAC AGGAGAATCA CCAGTGGCAA ATGTCCCCAG AAAGCTGTGA TGTAAGTAAA TAAAGTTCAC CCTCCCCTAG ACAAAAAAT AATGTCTAGG GCACAGAGTC AAGAACTGTG GGAGTCATAG ACTCTGATAG TTTGACCTCT ATGGTCCAAT TCATTAATTT TCACAAGTGA GTGTTCACTC CCAGCTCCCT GCCTGGGAGA TTGCTGTAGT CATATCAATT TCTTCAAGTC AAGAGCAAAG ATGGTTTTAC TGGGCCTTTA AGAGCAGCAA CTAACCCAAG AGTCTCATCC TTCCTCCTCT CCGTAGCAAC CCTTTGTCCA GGGGCAGATG GTCCTTAAAT ATTTAGGGTC AAATGGGCAG AATTTTCAAA AACAATCCTT CCAATTGCAT CCTGATTCTC CCCACAGCTT CAAGACCAAA CTGGCCAAGG ATATCTGTGC CGACCCCAAG AAGAAGTGGG TGCAGGATTC GAGCCTGAGT GTTGCCTAAT TTGTTTTCCC TTCTTACAAT GCATTCTGAG GTAACCTCAT TATCAGTCCA AAGGGCATGG GTT TATTAT ATATATAT ATATATTTT TTTTAAAAAA AAACGTATTG CATTTAATTT ATTGAGGCTT TAAAACTTAT CCTCCATGAA TATCAGTTAT TTTTAAACTG TAAAGCTTTG TGCAGATTCT TTACCCCCTG GGACICCCCAA TTCGATCCCC TGTCACGTGT GGGCAATGTT CCCCCTCTCC TCTCTTCCTC CCTGGAATCT TGTAAAGGTC CTGGCAAAGA TGATCAGTAT GAAAATGTCA TTGTTCTTGT GAACCCAAAG TGTGACTCAT TAAATGGAAG TAATGTTGTT TTAGGAATAC ATAAAGTATG TGCATATTTT ATTATAGTCA CTAGTTGTAA TTTTTTTGTG GGAAATCCAC ACTGAGCTGA GGGGG-3' (FRAG.NO: ) NO:2494) 5'-GCATTTTTC AACITTTATG ATTTATTTAA CTTGTGGAAC AAAAATAAAC CAGAAACCAC CACCTCTCAC GCCAAAGCTC ACACCTTCAG CCTCCAACAT GAAGGTCTCC GCAGCACTTC TGTGGCTGCT GCTCATAGCA GCTGCCTTCA GCCCCCAGGG GCTCGCTGGG CCAGCTTCTG TCCCAACCAC CTGCTGCTTT AACCTGGCCA



## FK-506 Binding Frotein Nucleic Acids and Oligonucleotide Fragments

55 5'- GCCAGGTCGC TGITGGTCCA CGCCGCCGT CGCGCCGCC GCCCGCTCAG CGTCCGCCGC CGCCATGGGA
GGCCGGAGCC GAGCCGGGGT CGGGCAGCAG CAGGGACCC CCAGAGGCGG GGCCTGTGG ACCGCTATGG
GCGTGGAGAT CGACACCATC TCCCCCGGAG ACGGAAGGAC ATTCCCCAAG AAGGGCCAAA CGTGTGTGGT
GCACTACACA GGA≜TGCTC AAAATGGGAA GAAGTTTGAT TCATCCAGAG ACAGAAACAA ACCTTTCAAG
TTCAGAATTG GCAAACAGGA AGTCATCAAA GGTTTTGAAG AGGGTGCAGC CCAGATGAGC TTGGGGCAGA
GGGCGAAGCT GACCTGCACC CCTGATGTGG CATATGGAGC CACGGGCCAC CCCGGTGTCA TCCCTCCCAA
TGCCACCCTC ATCT↑TGACG TGGAGCTGCT CAACTTAGAG TGAAGGCAGG AAGGAACTCA AGGTGGCTGG



5'- GCCAGGTCGC TG'TTGGTCCA CGCCGCCCGT CGCGCCGCCC GCCCGCTCAG CGTCCGCCGC CGCCATGGGA-3' (FRAG. No: )(SEQ. ID NO: 2495)

5'-GGCCGGAGCC GA3CCGGGGT CGGCCAGCAG CAGGGACCCC CCAGAGGCGG GGCCTGTGGG CCGCTATGG
GCGTGGAGAT CGACACCATC TCCCCCGGAG ACGGAAGGAC ATTCCCCAAG AAGGGCCAAA CGTGTGTGGT
GCACTACACA GGAATGCTC AAAATGGGAA GGAGTTTGAT TCATCCAGAG ACGAAAACAA ACCTTTCAAG
TTCAGAATTG GCAAACAGGA AGTCATCAAA GGTTTTGAAG AGGGTGCAGC CCAGATGAGC TTGGGGCAGA
GGGCGAAGCT GACCTGCACC CCTGATGTGG CATATGGAGC CACGGGCCAC CCCGGTGTCA TCCCTCCCAA
TGCCACCCTC ATCTTTGACG TGGAGCTGCT CAACTTAGAG TGAAGGCAGG AAGGAACTCA AGGTGGCTGG
AGATGGCTGC TGCTCACCCT CCTAGCCTGC TCTGCCCACTG GGACGGCTCC TGCTTTTGGG GCTCTTGATC
AGTGTTCATG CGAATTCTTG CTTGAGGAAA CTTCGGTTGC AGATTGAAGC ATTTCAGGTT GTGCATTTTG
TGTGATGCAT GTAGTAGCCT TCCTGATGA CAGAACACAG ATCTCTTGTT CGCACAATCT ACACTGCCTT
ACCTTCACTT AAACCACACA CACAAGGTGC TCAGACATGA AATGTACATG GCGTACCGTA CACAGAGGGA
CTTGAGCCAG TTACCTTTCC TGTCACTTT TCTCTTATAA ATTCTGTTAG CTGCTCACTT AAACCACTC
CTCTTTGAGA AAATGTAAAAA TAAAGGCTCT GTGCTTTGACA-3'(FRAG. NO:)) (SEQ. ID NO:2496)

5'-GAATTCGGGC CGI:CGCCAGG TCGCTGTTGG TCCACGCCGC CCGTCGCGCC GCCCGCCCGC TCAGCGTCCG

5CGCCGCCAT GGGAGTGCAG GTGGAAACCA TCTCCCCAGG AGACGGGCG ACCTTCCCCA AGCGCGCCA
GACCTGCGTG GTGCACTACA CCGGGATGCT TGAAGATGGA AAGAAATTTG ATTCCTCCCG GGACAGAAAC
AAGCCCTTTA AGTT'IATGCT AGGCAAGCAG GAGGTGATCC GAGGCTGGGA AGAAGGGGTT GCCCAGATGA
GTGTGGGTCA GAGAGCCAAA CTGACTATAT CTCCAGATTA TGCCTATGGT GCCACTGGGC ACCCAGGCAT
CATCCCACCA CATGCCACTC TCGTCTTCGA TGTGGAGCTT CTAAAACTGG AATGACAGGA ATGGCCTCCT

60 CCCTTAGCTC CCTGTTCTTG GATCTGCCAT GGAGGGATCT GGTGCCTCCA GACATGTGCA CATGAGTCCA
TATGGAGCTT TTCCIGATGT TCCACTCCAC TTTGTATAGA CATCTGCCCT GACTGATTTAC CTAAACTATA

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CTC/AGTTAT TCATTTTATT TTGTTTTCAT TTTGGGGTGA AGATTCAGTT TCAGTCTTTT GGATATAGGT TTCCAATTAA GTACATGGTC AAGTATTAAC AGCACAAGTG GTAGGTTAAC ATTAGAATAG GAATTGGTGT TGGGGGGGG GTTTGCAAGA ATATTTTATT TTAATTTTTT GGATGAAATT TTTATCTATT ATATATTAAA CATTCTTGCT GCTGCGCTGC AAAGCCATAG CAGATTTGAG GCGCTGTTGA GGACTGAATT ACTCTCCAAG TTGAGAGATG TCTTTGGGTT AAATTAAAAG CCCTACCTAA AACTGAGGTG GGGATGGGGA GAGCCTTTGC CTCCACCATT CCCACCCACC CTCCCCTTAA ACCCTCTGCC TTTGAAAGTA **GATCATGTTC** ACTGCAATGC TGGA CACTAC AGGTATCTGT CCCTGGGCCA GCAGGGACCT CTGAAGCCTT **CTTTGTGGCC** TTTTTTTTT TTCATCCTGT GGTTTTTCTA ATGGACTTTC AGGAATTTTG TAATCTCATA **ACTTTCCAAG** CTCCACCACT TCCTAAATCT TAAGAACTTT AATTGACAGT TTCAATTGAA GGTGCTGTTT **GTAGACTTAA** CACCCAGTGA AAGCCCAGCC ATCATGACAA ATCCTTGAAT GTTCTCTTAA GAAAATGATG CTGGTCATCG CAGCTTCAGC ATC1'CCTGTT TTTTGATGCT TGGCTCCCTC TGCTGATCTC **AGTTTCCTGG** CTTTTCCTCC TCTCACCCCT TTGCTGTCCT GTGTAGTGAT TTGGTGAGAA ATCGTTGCTG CTCAGCCCCT CACCCTTCCC CCAGCACCAT TTATGAGTCT CAAGTTTTAT TATTGCAATA AAAGTGCTTT ATGCCCGAAT TC-3' (FRAG.NO: ) (SEQ. ID NO:2497)

15 5' GCCGCCGCCA TGGGAGTGCA GGTGGAAACC ATCTCCCCAG GAGACGGCGC CACCTTCCCC AAGCGCGGCC AGACCTGCGT GGTCCACTAC ACCGGGATGC TTGAAGATGG AAAGAAATTT GATTCCTCCC GGGACAGAAA CAAGCCCTTT AAGTITATGC TAGGCAAGCA GGAGGTGATC CGAGGCTGGG AAGAAGGGT TGCCCAGATG AGTGTGGGTC AGACIAGCCAA ACTGACTATA TCTCCAGATT ATGCCTATGG TGCCACTGGG CACCCAGGCA TCATCCCACC ACATGCCACT CTCGTCTTCG ATGTGGAGCT TCTAAAACTG GAATGACAGG AATGGCCTCC 20 TCCCTTAGCT CCCTGTTCTT GGATCTGCCR TGGAGGGATC TGGTGCCTCC AGACATGTGC ACATGARTCC ATATGGAGCT TTTCCTGATG TTCCACTCCA CTTTGTATAG ACATCTGCCC TGACTGAATG TGTTCTGTCA CTCAGCTTTG CTTCCGACAC CTCTGTTTCC TCTTCCCCTT TCTCCTCGTA TGTGTGTTTA CCTAAACTAT ATGCCATAAA CCTCAAGTTA TTCA-3' (FRAG. NO: ) (SEQ. ID NO:2498)

wherein B is adenosine, or, more preferably, replaces adenosine and is an "equivame\lent" or a "universal" base, and adenosine  $A_{2a}$  receptor agonist or only minimally antagonist, an adenosine  $A_{2b}$  receptor antagonist, an adenosine  $A_3$  receptor antagonist, or an adenosine  $A_1$  receptor antagonist. Similarly, adenosine (A) may always be replaced by an "alternative", "equivalent" and/or "universal" base having a smal fraction, preferably less than 0.3 of the activity of adenosine at the adenosine receptor(s), as described above.

In one preferred embodiment, the links between neighboring mononucleotides are phosphodiester links. In another preferred, at least one mononucleotide phosphodiester residue of the anti-sense oligonucleotide(s) is substituted by a methylphosphonate, phosphotriester, phosphorothioate, phosphorodithioate, poranophosphate, formacetal, thioformacetal, thioether, carbonate, carbamate, sulfate, sulfonate, sulfamate, sulfonamide, sulfone, sulfite, sulfoxide, sulfide, hydroxylamine, 2'-O-methyl, methylene(methyimino), methyleneoxy (methylimino), phosphoramidate residues, and combinations thereof. The oligos having one or more phosphodiester residues substituted by one or more of the other residues are general y longer lasting, given that these residues are more resistant to hydrolysis than the phosphodiester residue. In some cases up to about 10%, about 30%, about 50%, about 75%, and even all phosphodiester residues may be substituted (100%). Typically, the multiple target anti-sense oligonucleotide (oligo) of the invention comprises at least about 7 mononucleotides, in some instances up to 60 and more mononucleotides, preferably about 10 to about 36, and more preferably about 12 to about 21 mononucleotides. However, other lengths are also suitable depending on the length of the target macromolecule. Examples of the MTA oligos of the invention are provided in Table 3 below, which includes ninety-four sequences (SEQ ID NOS.: 2316 through 2410).

Table 3:	Table 3: MTA Oligos, Location Targeted & Target				
MTA Oligo	SEQ. ID	Location	Compound	Target	
	No.		Targeted		
HUMNFKBP65A AS					
CCC GGC CCC GCC TCG TGC C	3019	5′=1	EPI 2192		
CGT CCB TGC CGC GGG CCC	3020	5′=28(AU	G)EPI 2193		
GCC CCG CTG CTT GGG CTG CTC TGC CGC	g G 3021	5′=65	EPI 2194		
TCT GTG CTC CTC TCG CCT GGG	3022	5'=137	EPI 2195		
TGG TGG GGT GGG TCT TGG TGG	3023	5'=159	EPI 2196		
CTG TCC CTG GTC CTG TG	3024	5'=196	EPI 2197		

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	GGT CCC GCT TCT TC	3025	5'=362 EPI 2198
	GGG GTT GTT GTT CTG G	3026	5'=401 EPI 2199
	TGT CCT CTT TCT GC	3026	5'=656 EPI 2200
	GCC TCG GGC CTC CC	3027	5'=697 EPI 2201
5	GGC TGG GGT CTG CGT	3028	5'=769 EPI 2202
	GGC CGG GGG TCG GTG GGT CCG CTG	3029	5'=953 EPI 2203
	GGG CTG GGG TGC TGG CTT GGG G	3030	5'=1022 EPI 2204
	GGG GCT GGG GCC TGG GCC	3031	5'=1208 EPI 2205
	GCC TGG GTG GGC TTG GGG GC	3032	5'=1272 EPI 2206
10	GCT GGG TCT GTG CTG TTG CC	3033	5'=1362 EPI 2207
	GTT GTG TGG GGG GCC	3034	5'= 1451 EPI 2208
	GCT GGG TCG GGG GGC CTC TGG GCT GTC		5'=1511 EPI 2209
	GCC CCG GGG CCC CC	3036	5'=1550 EPI 2210
	TGG CTC CCC CCT CC	3037	5'=1772 EPI 2211
15	GCT CCC CCC TTT CC	3038	5'=1863 EPI 2212
	CGG ACG AAG ACA GAG A	3039	5'=1979 EPI 2213
	GGC TTT GTG GGC TC	3040	5'=2011 EPI 2214
	GCC TGC TCT CCC CC	3041	5'=2312 EPI 2215
	CCC GGC CCC GCC BCG BBC C	3042	intron EPI 2192-01A HSU50136C4Synth
20	CCC GGC CCC GCC BCG	3043	intron EPI 2192-01B
	CCC GGC CCC GCC BCG BBC C	3044	5'untr EPI 2192-02A HUMLIPOX5LO
	CCC GGC CCC GCC BCG	3045	5'untr EPI 2192-02B
	CCC GBC CCC GCC TCB BG	3046	trans EPI 2192-03A HSNFKBS Subunit
	CCC GBC CCC GCC TC	3047	trans EPI 2192-03B
25	CCG GCC CCG CCT C	3048	5'untr EPI 2192-04 TGFβR1
	CCC GBB CCC GCB TBG TGC C	3049	5'trans EPI 2192-05A HSU5819811 enhan
	CCC GCB TBG TGC C	3050	5'untr EPI 2192-05B
	CCC GGB CCC BCC BBG TGC C	3051	3'trans EPI 2192-06 HSVECAD
	CBG BBC CCG CCT CGT GCC	3052	intron EPI 2192-07A NFKB2
30	C CCG CCT CGT GCC	3053	intron EPI 2192-07B NFKB2
	CCG GCB CCG CCT CBT GCC	3054	5'trans EPI 2192-08 Carboxypep
	CCG GCC CCG CCB CBT GCC	3055	3'trans EPI 2192-09 HumADRA2Cα2AdrKid
	CCC GBC CCC GBC TCG	3056	5'untrs EPI 2192-10 HUMFK506B
	CCC GGC CBC GBC TCG	3057	5'untrs EPI 2192-11 HSNBARKS1βAdrKin
35	CCC GGC CCB GCC TBG	3058	5'UTR EPI 2192-12 HSNFXN1(NFKB1)
	CCC GGC BCB GBC TCG TBC C	3059	3'UTR EPI 2192-13 HSILF(transcrp.
			Factor ILF)
	CCC GGC CCC GCC BCG	3060	EPI-2192-14 NFKB/C4Syn/5-LO/
40			TGFBrec1 MTA
40	CCC GGC CCC GCC BCG	3061	EPI-2192-15NFKB/C4Syn/5-LOMTA
	TCC BTG CCG CGG GC	3062	3' trans EPI-2193-01 METOncogene
	TCC BTG CCB CGG GCC	3063	3' trans EPI-2193-02 HSFGR2(IG)
	TCC BTG CCB CGG GCC	3064	mid cod EPI-2193-03 5-LO
45	TCC BTG CCB CBG GCC	3065	mid cod EPI-2193-04 HUMTK14
45 ,	GTC CBT GBC GCG G	3066	3'trans EPI-2193-05 HUMTNFR
	TC CBT GBC GCG (iG	3067	AUG Probl.HUMPTCH
	MOM CDG CMG CMG MDD CCM CCG	2060	cardiacK+channel
	TCT GBG CTC CTC TBB CCT GGG	3068	intr EPI-2195-01 humCSPAcytotox.
50	CTC TCC BCC TBB CBC CTC CC	2000	Ser.Protease
50	CTG TGC BCC TBB CBC CTG GG TGT GBT CCB CTB GBC TGG G	3069	intr EPI-2195-02 HSINOSX08induc.NOS EPI-2195-03 HUMACHRM2musc.m2
	IGI GDI CCD CID GDC IGG G	3070	EPI-2195-03 HUMACHRM2musc.m2 acetylch.rec.
	TCT GTB CTC BBC TCB CCT G	3071	EPI-2195-04 s86371s1
	101 31 <b>2</b> 010 <b>22</b> 0 10 <b>3</b> 001 G	3011	Neurokinin3Recept
55	TGC TCC TCB CBB CTG GG	3072	EPI-2195-05 HUMMIP1 Amacro
	inflam.factor		

Table 3: MTA Oligos, Location Targeted & Target (Cont'd)

MTA Oligo			SEQ. ID No.	Location	Compound Targeted	Target
CTC CTC TBG CCT	GG		3073	·	EPI-2195-06	HSNBARKS4
						β-Adr Rec Kinase
GTG CTC CBB TCB	BCT	GGG	3074		EPI-2195-07	HSTNFR2SO6TNF R2
GTG CBC CBB TCB	CCT	GGG	3075		EPI-2195-08 1	
	~	_ ~~	2056			oinding prot.
TCT GTG CBC CTC	TBG	BCT	3076	exon	EP1-2195-09 E	ISNBARKS1β-Adr. Recept.Kinase
CTG TBB TCC TBB	CBC	ста а	3077	intron	EPI-2195-10	HUMIL8
TGT GCT BBT CBC			3078	11101011	EPI-2195-11	HSU50157 PDE4
GTG CBC CBC TCB			3079	intron/exon	EPI-2195-12	IL-2 R
CTG TGC BCC TCT			3080	3'UTR	EPI-2203-05	IL-6 R HSIL6R
CBG TGC BCC BCT	CBC	CTG	3081	intr/ex	EPI-2203-06A	HSIL2rG6
G TGC BCC BCT C	E/C C	TG	3082	intr/ex	EPI-2203-06B	HSIL2rG6
CBC CTC TCB CCT	GGG		3083	coding	EPI-2203-07A	HUMIL71
C CTC TCB CCT G	G		3084	coding	EPI-2203-07B	IL-7 HUMIL71
GCT CCB CTC GCC			3085	coding	EPI-2203-08	IL-6 R HSI6REC
TGC TCC TCB CGC			3086		A EPI-2303-09	Chain HUMPDGFAB
GTT GTT GBT CTG	G		3087	3'utr	EPI-2199-01	GATA-4Transcrip.
	m <	maa	2000	O = 2	EDT 0100 00	Factor for IL-5
GGT TGB BBT TGG GGT TGT TGB TGB			3088 3089	Coding	EPI-2199-02 EPI-2199-03	TNFα HUMTNFA HSSUBP1G(Sub Pr)
GGT TGT TGB TGB			3089	Coding	EPI-2199-03 EPI-2199-04	NeutrophilAdh.
פון פעם בון פפט	יום	100	3090	Coding	EFI ZIJJ 04	R HUMNARIA
GGG TTB BBG TTG	BTC	TGG	3091	HSHM2	EPI-2199-05	m2 Muscarinic R
TTG TTG TBG BTC			3092	HUML1CAM	EPI-2199-06	Ll LeukAadhProt
GGG TBG BBG BGT	CCG	CTG	3093	coding	EPI-2203-01	HUMGATA2A
GGG TCB GBG GBT	C <b>B</b> G	CTG	3094	S71424S2	EPI-2203-02	IGE eps
GGG TBG GTG GGT	C		3095	coding	EPI-2203-03	HSGCSFR2
GGG TCG GBG GGT	CBG	C	3096	HUMITGF	EPI-2203-04	TGFβ3
GGG TGG GCT T			3097	HUMNK65PR	O EPI-2206-01	TCell
GGG TGG GCT TGG	C		3098	CHACHCHIL	Activ EPI 2206-02	ating Prot NFKB/Prostagl.
666 166 661 166	G		3096	HUMPEREED	EPI 2206-02	EP3 Rec
CCTGGGTGGGBBTGG	C‡		3099		EPI 2206-03	
001000100022100	.,		3033			FKB/GranuLocCSF/
						ranscr.FactorNF2B
CCTGGBTGGGCBTGG	C}		3100		EPI-2206-04	•
CCCMCDCMCDDCMC	cic.		2101		Leu EPI2206-05 1	k.Adhes.Prot
GCCTGBGTGBBCTTG	خان		3101		₽₽17700-02 [	NFKB/Endothel
CCCAVGVCCVCCCAG	CiC		3102		EPT 2206-06	NZ S63833 NFKBAS13/B Lymph
CCCIVO V CC V CCCAG	.,_		3102			SerThrProt.Kinase
AGCCCACCCAGGC			3103		EPI2206-07	NFKBAS13/GCSF1
						HSGCSFR1Rec
BCCTGGGTGGGCTB			3104		EPI2206-08 N	
GGTGGGCTTGGG			3105		EPI 2206-09	NK7TCELLACT.Prot NFKBAS13/
001000011000			3103		HII 2200 05	HSTGFB1 TGFB
CCBBGGTGGGCTTGG	(}		3106		EPI 2206-10	NFKBAS13/
						HSTGFB1 TGFB1
CTGGGTGGGBBTGGG			3107		EPI 2206-11	•
					cood 10	HSGCSFR1 GCSFR1
aanaaamaaa			3108			NFKBAS13/HUMCD30A mphActAntigCoding
CCBGGGTGGGCTTGG					ШУ	INDITACE CATTE TACOUTIIA
			3109	म	PI-2206-12B	
GGGTGGGCTTGG	( <del>}</del>		3109 3110	Е		NFKBAS13/HUMCD30A
	(}		3109 3110	Е		

The MTA oligos of Table 3 are suitable for use with two or more of the targets listed in Table 4 below.

Table 4: Targets for the MTA Oligos of Table 3

Compound	Target
EPI 2010	Adenosine A1 receptor
EPI 2045	Adenosine A3 receptor
EPI 2873, EPI 2193	NFκB
EPI 1873	Interleukın-l
EPI 1857	Interleukın -5
EPI 2945	Interleukın -4
EPI 2977	Interleukin -8
EPI 2031	5-Lipoxygenase
EPI 1898	Leukotriene C-4 Synthase
EPI 1856	Eotaxin
EPI 1131	ICAM
EPI 1085	VCAM
EPI 2085	TNFα
EPI 1908	PAF
EPI 1925	IL-4 receptor
EPI 2643	β2 aderenergic receptor kinase
EPI 2934	Tryptase
EPI 2033	Major Basic Protein
EPI 2795	Eosinophil Peroxidase

NfκB: nuclear factor κB

ICAM: intracellular adhesion molecule VCAM: vascular cell adhesion molecule

TNF: tumor necrosis factor PAF: platelet activating factor

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The mRNA sequence of the targeted protein may be derived from the nucleotide sequence of the gene expressing the protein, whether for existing targets or those to be found in the future. Sequences for many target genes of different systems are presently known. See, GenBank data base, NIH, the entire sequences of which are incorporated here by reference. The sequences of those genes, whose sequences are not yet available, may be obtained by isolating the target segments applying technology known in the art. Once the sequence of the gene, its RNA and/or the protein are known, anti-sense oligonucleotides are produced as described above and utilized to validate the target by in vivo administration and testing for a reduction of the procuction of the targeted protein in accordance with standard techniques, and of specific functions. As already described above, the anti-sense oligonucleotides may be of any suitable length, e.g., from about 7 to about 60 nucleotides in length, depending on the particular target being bound and the mode of delivery thereof. The anti-sense oligonucleotide preferably is directed to an mRNA region containing a junction between intron and exon or to regions vicinal to the junction. Where the anti-sense oligonucleotide is directed to an intron/exon junction, it may either entirely overlie the junction or may be sufficiently close to the junction to inhibit splicing out of the intervening exon during processing of precursor mRNA to nature mRNA, e.g., with the 3' or 5' terminus of the anti-sense oligonucleotide being positioned within about, for example, 10, 5, 3, or 2 nucleotide of the intron/exon junction. Also preferred are anti-sense oligon icleotides which overlap the initiation codon and, more generally, those that target the coding region of the target mRNA. When practicing the present invention, the anti-sense oligonucleotides administered may be related in origin to the species to which it is administered. When treating humans, human anti-sense may be used if desired. Anti-sense oligos to endogenous sequences from other species,

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however, are also encompassed.

Pharmaceutical compositions comprising an anti-sense oligonucleotide as given above effective to reduce expression of an A1 or A3 adenosine receptor by passing through a cell membrane and binding specifically with mR NA encoding an A<sub>1</sub> or A<sub>3</sub> adenosine receptor in the cell so as to prevent its translation are another aspect of the present invention. Such compositions are provided in a suitable pharmaceutically acceptable carrier, e.g., sterile pyrogen-free saline solution. The anti-sense oligonucleotides may be formulated with a hydrophobic carrier capable of passing through a cell membrane, e.g., in a liposome, with the liposomes carried in a pharmaceutically acceptable aqueous carrier. The oligonucleotides may also be coupled to a substance which inactivates mRNA, such as a ribozyme. Such oligonucleotides may be administered to a subject to inhibit the activation of a target, such as the adenosine receptors, which subject is in need of such treatment for any of the reasons discussed herein. Furthermore, the pharmaceutical formulation may also contain chimeric molecules comprising anti-sense oligonucleotides attached to molecules which are known to be internalized by cells. These oligonucleotide conjugates utilize cellular uptake pathways to increase cellular concentrations of oligonucleotides. Examples of macromolecules used in this manner include transferrin, asialoglycoprotein (bound to oligonucleotides via polylysine) and streptavidin. In the pharmaceutical formulation, the anti-sense compound may be contained within a lipid particle or vesicle, such as a liposome or microcrystal. The particles may be of any suitable structure, such as unilamellar or plurilamellar, so long as the anti-sense oligonucleotide is contained therein. Positively charged lipids such as N- [1-(2, 3 -dioleoyloxi) propyl] -N, N, N-trimethylammoniumethylsulfate, or "DOTAP," are particularly preferred for such particles and vesicles. The preparation of such lipid particles is well known. See, e.g., U.S. Patent Nos. 4,880,635 to Janoff et al.; 4,906,477 to Kurono et al.; 4,911,928 to Wallach; 4,917,951 to Wallach; 4,920,016 to Allen et al.; 4,921,757 to Wheatley et al.; etc.

Subjects may be administered the active composition by any means which transports the antisense nucleotide composition to the lung. The antisense compounds are particularly disclosed herein may be administered to the lungs of a patient by any suitable means, but are preferably administered by generating an aerosol comprised of respirable particles, the respirable particles comprised of the antisense compound, which particles the subject inhales. The respirable particles may be liquid or solid. The particles may optionally contain other therapeutic ingredients. Particles comprised of antisense compound for practicing the present invention should include particles of respirable size: that is, particles of a size sufficiently small to pass through the mouth and larynx upon inhalation and into the bronchi and alveoli of the lungs. In general particles ranging from about .5 to about 10 microns in size are respirable. Particles of non-respirable size which are included in the aerosol tend to deposit in the throat and be swallowed, and the quantity of non-respirable particles in the aerosol is preferably minimized. For nasal administration, a particle size in the range of 10-500 :m is preferred to ensure retention in the nasal cavity. Thus, particles of about 4, about 10, about 25, about 50 to about 75, about 100, about 250, about 500, and other specific ranges therewithin, are preferred. Others, however, are also contemplated within the confines of this invention.

Liquid pharmaceutical compositions of active compound for producing an aerosol can be prepared by combining the anti-sense compound with a suitable vehicle, such as sterile pyrogen free water. Other therapeutic compounds may optionally be included. Solid particulate compositions containing respirable dry particles of mic onized anti-sense compound may be prepared by grinding dry anti-sense compound with a mortar and pestle, and then passing the micronized composition through a 400 mesh screen to break up or separate out large agglomerates. A solid particulate composition comprised of the anti-sense compound may optionally contain a dispersant which serves to facilitate the formation of an aerosol. A suitable dispersant is lactose, which may be blended with the anti-sense compound in any suitable ratio (e.g., a 1 to 1 ratio by weight). Again, other therapeutic compounds may also be included.

The dosage of the anti-sense compound administered will depend upon the disease being treated, the condition of the subject, the particular formulation, the route of administration, the timing of administration to a subject, etc. In general, intracellular concentrations of the oligonucleotide of from about

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0.01, about 0.05, about 0.1, about 0.2, about 1 to about 5 µM, about 50 µM, about 100 µM or more, and more particularly about 0.2 to about 0.5 μM, are desired. For administration to a subject such as a human, a dosage of from about 0.01, about 0.1 or about 1 mg/Kg up to about 50, about 100, or about 150 mg/Kg and even higher doses are typically employed depending on the route of administration as is known in the art. Depending on the solubility of the particular formulation of active compound administered, the daily dose may be divided among one or several unit dose administrations. Administration of the anti-sense compounds may be carried out therapeutically (i.e., as a rescue treatment) or prophylactically. Aerosols of liquid particles comprising the anti-sense compound may be produced by any suitable means, such as with a nebulizer. See, e.z., U.S. Patent No. 4,501,729. Nebulizers are commercially available devices which transform solutions or suspensions of the active ingredient into a therapeutic aerosol mist either by means of acceleration of a compressed gas, typically air or oxygen, through a narrow venturi orifice or by means of ultrasonic agitation. Suitable formulations for use in nebulizers consist of the active ingredient in a liquid carrier, the active ingredient comprising up to 40% w/w of the formulation, but preferably less than 20% w/w. The carrier is typically water or a dilute aqueous alcoholic solution, preferably made isotonic with body fluids by the addition of, for example, sodium chloride. Optional additives include preservatives if the formulation is not prepared sterile, for example, methyl hydroxybenzoate, antioxidants, flavoring agents, volatile oils, buffering agents and surfactants.

In one preferred embodiment, the pharmaceutical composition comprises nucleic acid(s) which comprise the anti-sense oligo(s) described above and one or more surfactants. Suitable surfactants or surfactant components for enhancing the uptake of the anti-sense oligonucleotides of the invention include synthetic and natural as well as full and truncated forms of surfactant protein A, surfactant protein B, surfactant protein C, surfactant protein D and surfactant Protein E, di-saturated phosphatidylcholine (other dipalmitoylphosphatidylcholine, phosphatidylcholine, phosphatidylglycerol, dipalmitoyl). phosphatidylinositol, phosphatidylethanolamine, phosphatidylserine; phosphatidic acid, ubiquinones, lysophosphatidylethe nolamine, lysophosphatidylcholine, palmitoyl-lysophosphatidylcholine, dehydroepiandrosterone, dolichols, sulfatidic acid, glycerol-3-phosphate, dihydroxyacetone phosphate, glycerol, glycero-3-phosphocholine, dihydroxyacetone, palmitate, cytidine diphosphate (CDP) diacylglycerol, CDP choline, choline, choline phosphate; as well as natural and artificial lamellar bodies which are the natura carrier vehicles for the components of surfactant, omega-3 fatty acids, polyenic acid, polyenoic acid, leci hin, palmitinic acid, non-ionic block copolymers of ethylene or propylene oxides, polyoxypropylene, rionomeric and polymeric, polyoxyethylene, monomeric and polymeric, poly (vinyl amine) with dextran and/or alkanoyl side chains, Brij 35, Triton X-100 and synthetic surfactants ALEC, Exosurf, Survan and Atovaquone, among others. These surfactants may be used either as a single, or as part of a multiple co nponent, surfactant in a formulation, or as covalently bound additions to the 5' and/or 3' ends of the anti-sense oligo(s). Aerosols of solid particles comprising the active compound may likewise be produced with any solid particulate medicament aerosol generator. Aerosol generators for administering solid particulate medicaments to a subject produce particles which are respirable, as explained above, and generate a volume of aerosol containing a predetermined metered dose of a medicament at a rate suitable for human administration. One illustrative type of solid particulate aerosol generator is an insufflator. Suitable formulations for administration by insufflation include finely comminuted powders which may be delivered by means of an insufflator or taken into the nasal cavity in the manner of a snuff. In the insufflator, the powder (e.g., a metered dose thereof effective to carry out the treatments described herein) is contained in capsules or cartridges, typically made of gelatin or plastic, which are either pierced or opened in situ and the powder delivered by air drawn through the device upon inhalation or by means of a manually-operated pump. The powder employed in the insufflator consists either solely of the active ingredient or of a powder blend comprising the active ingredient, a suitable powder diluent, such as lactose, and an optional surfactant. The active ingredient typically comprises from 0.1 to 100 w/w of the formulation. A second type of illustrative aerosol generator comprises a metered dose inhaler. Metered dose inhalers are pressurized aerosol dispensers, typically containing a suspension or

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solution formulation of the active ingredient in a liquefied propellant. During use these devices discharge the formulation through a valve adapted to deliver a metered volume, typically from 10 to 150 :l, to produce a fine particle spray containing the active ingredient. Suitable propellants include certain chlorofluorocarbon compounds, for example, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroet ane and mixtures thereof. The formulation may additionally contain one or more cosolvents, for example, ethanol, surfactants, such as oleic acid or sorbitan trioleate, antioxidants and suitable flavoring agents. The aerosol, whether formed from solid or liquid particles, may be produced by the aerosol generator for example at a rate of from about 10, about 30, about 70 to about 100, about 150, about 150 liters per minute, more preferably from about 30 to 150 liters per minute, and most preferably about 60 liters per minute. Aerosols containing greater amounts of medicament, however, may be administered more rapidly as is known in the art.

The relevant disclosures of all scientific publications and patent references cited in this patent are specifically intended to be incorporated herein by reference, particularly in reference to preparatory methods and technologies which are enabling of the invention. The following examples are provided to illustrate the present invention, and should not be construed as limiting thereon.

### **EXAMPLES**

In the following examples, :M means micromolar, ml means milliliters, :m means micrometers, mm means millimeters, cm means centimeters, EC means degrees Celsius, :g means micrograms, mg means milligrams, g means grams, kg means kilograms, M means molar, and h or hr. means hours.

### 20 Example 1: Design and Synthesis of Anti-sense Oligonucleotides

The design of anti-sense oligonucleotides against the  $A_1$  and  $A_3$  adenosine receptors may require the solution of the complex secondary structure of the target  $A_1$  receptor mRNA and the target  $A_3$  receptor mRNA. After generating this structure, anti-sense nucleotide are designed which target regions of mRNA which might be construed to confer functional activity or stability to the mRNA and which optimally may overlap the initiation codon. Other target sites are readily usable. As a demonstration of specificity of the anti-sense effect, other oligonucleotides not totally complementary to the target mRNA, but containing identical nucleotide compositions on a w/w basis, are included as controls in anti-sense experiments.

The mRNA secondary structure of the adenosine A<sub>1</sub> receptor was analyzed and used as described above, to design a phosphorothioate anti-sense oligonucleotide. The anti-sense oligonucleotide which was synthesized was designated HAdA<sub>1</sub>AS and had the following sequence: 5'-GAT GGA GGG CGG CAT GGC GGG-3' (SEQ ID NO:1). As a control, a mismatched phosphorothioate anti-sense nucleotide designated HAdAlMM1 was synthesized with the following sequence: 5'-GTA GCA GGC GGG GAT GGG GGC-3' (SEQ ID NO:2). Each oligonucleotide had identical base content and general sequence structure. Homology searches in GENBANK (release 85.0) and EMBL (release 40.0) indicated that the anti-sense oligonucleotide was specific for the human and rabbit adenosine A<sub>1</sub> receptor genes, and that the mismatched control was not a candidate for hybridization with any known gene sequence.

The secondary structure of the adenosine A<sub>3</sub> receptor mRNA was similarly analyzed and used as described above to design two phosphorothioate anti-sense oligonucleotides. The first anti-sense oligonucleotide (HAdA3AS1) synthesized had the following sequence: 5' -GTT GTT GGG CAT CTT GCC-3' (SEQ ID NO:3). As a control, a mismatched phosphorothioate anti-sense oligonucleotide (HAdA3MM1) was synthesized, having the following sequence: 5' -GTA CTT GCG GAT CTA GGC-3' (SEQ ID NO:4). A second phosphorothioate anti-sense oligonucleotide (HAdA3AS2) was also designed and synthesized, having the following sequence: 5' -GTG GGC CTA GCT CTC GCC-3' (SEQ ID NO:5). Its control oligonucleotide (HAdA3MM2) had the sequence: 5' -GTC GGG GTA CCT GTC GGC-3' (SEQ ID NO:6). Phosphorothioate oligonucleotides were synthesized on an Applied Biosystems Model 396 Oligonucleotide Synthesizer, and purified using NENSORB chromatography (DuPont, MD).

**Example 2:** In Vivo Testing of Adenosine  $A_1$ 

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#### **Receptor Anti-sense Oligos**

The anti-sense oligonucleotide against the human  $A_1$  receptor (SEQ ID NO:1) described above, was tested for efficacy in an in vitro model utilizing lung adenocarcinoma cells HTB-54. HTB-54 lung adenocarcinoma cells were demonstrated to express the  $A_1$  adenosine receptor using standard northern blotting procedures and receptor probes designed and synthesized in the laboratory.

HTB-54 hu nan lung adenocarcinoma cells (106/100 mm tissue culture dish) were exposed to 5.0 :M HAdAlAS or HAdAlMM1 for 24 hours, with a fresh change of media and oligonucleotides after 12 hours of incubation. Following 24 hour exposure to the oligonucleotides, cells were harvested and their RNA extracted by standard procedures. A 21-mer probe corresponding to the region of mRNA targeted by the anti-sense (and therefore having the same sequence as the anti-sense, but not phosphorothioated) was synthesized and used to probe northern blots of RNA prepared from HAdAlAS-treated, HAdAlMM1-treated and non-treated HTB-54 cells. These blots showed clearly that HAdAlAS but not HAdAlMM1 effectively reduced human adenosine receptor mRNA by >50%. This result showed that HAdAlAS is a good candidate for an anti-asthma drug since it depletes intracellular mRNA for the adenosine A<sub>1</sub> receptor, which is involved in asthma.

### Example 3: In Vivo Efficacy of Adenosine A<sub>1</sub> Receptor Anti-sense Oligos

A fortuitous homology between the rabbit and human DNA sequences within the adenosine A<sub>1</sub> gene overlapping the initiation codon permitted the use of the phosphorothioate anti-sense oligonucleotides initially designed for use against the human adenosine A<sub>1</sub> receptor in a rabbit model. Neonatal New Zealand white Pasteurella-free rabbits were immunized intraperitoneally within 24 hours of birth with 312 antigen units/ml house dustmite (D. farinae) extract (Berkeley Biologicals, Berkeley, CA), mixed with 10% kaolin. Immunizations were repeated weekly for the first month and then biweekly for the next 2 months. At 3-4 months of age, eight sensitized rabbits were anesthetized and relaxed with a mixture of ketamine hydrochloride (44 nig/kg) and acepromazine maleate (0.4 mg/kg) administered intramuscularly. The rabbits were then laid supine in a comfortable position on a small molded, padded animal board and intubated with a 4.0-mm intratracheal tube (Mallinkrodt, Inc., Glens Falls, NY). A polyethylene catheter of external diameter 2.4 mm with an attached latex balloon was passed into the esophagus and maintained at the same distance (approximately 16 cm) from the mouth throughout the experiments. The intratracheal tube was attached to a heated Fleisch pneumotachograph (size 00; DOM Medical, Richmond, VA), and flow was measured using a Validyne differential pressure transducer (Model DP-45161927; Validyne Engineering Corp., Northridge, CA) driven by a Gould carrier amplifier (Model 11-4113; Gould Electronic, Cleveland, OH). The esophageal balloon was attached to one side of the differential pressure transducer, and the outflow of the intratracheal tube was connected to the opposite side of the pressure transducer to allow recording of transpulmonary pressure. Flow was integrated to give a continuous tidal volume, and measurements of total lung resistance (RL) and dynamic compliance (Cdyn) were calculated at isovolumetric and flow zero points, respectively, using an automated respiratory analyzer (Model 6; Buxco, Sharon, CT). Animals were randomized and on Day 1 pretreatment values for PC50 were obtained for aerosolized adenosine. Anti-sense (HAdAlAS) or mismatched control (HAdAlMM) oligonucleotides were dissolved in sterile physiological saline at a concentration of 5000 :g (5 mg) per 1.0 ml. Animals were subsequently administered the aerosolized anti-sense or mismatch oligonucleotide via the intratracheal tube (approximately 5000 :g in a volume of 1.0 ml), twice daily for two days. Aerosols of either saline, adenosine, or anti-sense or mismatch oligonucleotides were generated by an ultrasonic nebulizer (DeVilbiss, Somerse, PA), producing aerosol droplets 80% of which were smaller than 5 :m in diameter. In the first arm of the experiment, four randomly selected allergic rabbits were administered anti-sense oligonucleotide and four the mismatched control oligonucleotide. On the morning of the third day, PC50 values (the concentration of aerosolized adenosine in mg/ml required to reduce the dynamic compliance of the bronchial airway 50% from the baseline value) were obtained and compared to PC50 values obtained for these animals prior to exposure to oligonucleotide. Following a 1 week interval, animals were crossed

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over, with those previously administered mismatch control oligonucleotide now administered anti-sense oligonucleotide, and those previously treated with anti-sense oligonucleotide now administered mismatch control oligonucleotide. Treatment methods and measurements were identical to those employed in the first arm of the experiment. It should be noted that in six of the eight animals treated with anti-sense oligonucleotide, adenosine-mediated bronchoconstriction could not be obtained up to the limit of solubility of adenosine, 20 mg/ml. For the purpose of calculation, PC50 values for these animals were set at 20 mg/ml. The values given therefore represent a minimum figure for anti-sense effectiveness. Actual effectiveness was higher. The results of this experiment are illustrated in Table 5 below.

Table 5: Effect of Adenosine A<sub>1</sub> Receptor Anti-sense Oligo up on PC50 Values in Asthmatic Rabbits

Mismatch Control		A <sub>1</sub> Receptor Anti-sense Oligo	
Pre Oligonucleotide	Post Oligonucleotide	Pre Oligonucleotide	Post Oligonucleotide
$3.56 \pm 1.02$	$5.16 \pm 1.03$	$2.36 \pm 0.68$	>19.5 ± 0.34**

The results are presented as the mean (n=8) ± SEM.

The significance was determined by repeated-measures analysis of variance (ANOVA), and Tukev's protected test,

\*\*Significantly different from all other groups, p<0 01

In both arms of the experiment, animals receiving the anti-sense oligonucleotide showed an order of magnitude increase in the dose of aerosolized adenosine required to reduce dynamic compliance of the lung by 50%. No effect of the mismatched control oligonucleotide upon PC50 values was observed. No toxicity was observed in any animal receiving either anti-sense or control inhaled oligonucleotide. These results show clearly that the lung has exceptional potential as a target for anti-sense oligonucleotide-based therapeutic intervention in lung disease. They further show, in a model system which closely resembles human asthma, that downregulation of the adenosine  $A_1$  receptor largely eliminates adenosine-mediated bronchoconstriction in asthmatic airways. Bronchial hyperresponsiveness in the allergic rabbit model of human asthma is an excellent endpoint for anti-sense intervention since the tissues involved in this response lie near to the point of contact with aerosolized oligonucleotides, and the model closely simulates an important human disease.

### **Example 4:** Specificity of A<sub>1</sub>-adenosine Receptor Anti-sense Oligonucleotide

At the conc usion of the cross-over experiment of Example 3 above, airway smooth muscle from all rabbits was quantitatively analyzed for adenosine A<sub>1</sub> receptor number. As a control for the specificity of the anti-sense oligorucleotide, adenosine A2 receptors, which should not have been affected, were also quantified. Airway smooth muscle tissue was dissected from each rabbit and a membrane fraction prepared according to the method of Kleinstein et al. (Kleinstein, J. and Glossmann, H., Naunyn-Schmiedeberg's Arch. Pharmacol. 305: 191-200 (1978)), the relevant portion of which is hereby incorporated in its entirety by reference, with slight modifications. Crude plasma membrane preparations were stored at 70EC until the time of assay. Protein content was determined by the method of Bradford (M. Bradford, Anal. Biochem. 72, 240-254 (1976), the relevant portion of which is hereby incorporated in its entirety by reference). Frozen plasma membranes were thawed at room temperature and were incubated with 0.2 U/ml adenosine deaminase for 30 minutes at 37EC to remove endogenous adenosine. The binding of [3H] DPCPX (A1 receptor-specific) or [3H] CGS-21680 (A1 receptor-specific) was measured as previously described by Ali et al. (Ali, S. et al., J. Pharmacol. Exp. Ther. 268, Am. J. Physiol 266, L271-277 (1994), the relevant portion of which is hereby incorporated in its entirety by reference). The animals treated with adenosine A<sub>1</sub> anti-sense oligonucleotide in the cross-over experiment had a nearly 75% decrease in A<sub>1</sub> receptor number compared to controls, as assayed by specific binding of the A<sub>1</sub>-specific antagonist DPCPX. There was no change in adenosine A2 receptor number, as assayed by specific binding of the A<sub>2</sub> receptor-specific agonist 2- [p- (2-carboxyethyl)-phenethylamino] -5' - (N-ethylcarboxamido) adenosine (CGS-21630). This is illustrated in Table 6 below.

<u>Table 6</u>: Specificity of Action of Adenosine A<sub>1</sub>
Receptor Oligonucleotide Anti-sense

Mismatch Control Oligonucleotide

A<sub>1</sub> Anti-sense Oligonucleotide

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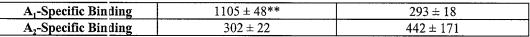
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The results are presented as the mean  $(n = 8) \pm SEM$ .

The significance was determined by repeated-measures analysis of variance (ANOVA), and Tukey's protected test \*\*Significantly different from mismatch control, p<0.01.

The above results illustrate the effectiveness of anti-sense oligonucleotides in treating airway disease. Since the anti-sense oligos described above, eliminate the receptor systems responsible for adenosine-mediated bronchoconstriction, it may be less imperative to eliminate adenosine from them. However, it would be preferable to eliminate adenosine from even these oligonucleotides to reduce the dose needed to attain a similar effect. Described above are other anti-sense oligonucleotides targeting mRNA of proteins it volved in inflammation. Adenosine has been eliminated from their nucleotide content to prevent its liberation during degradation.

#### **Example 5:** Anti-sense Oligos directed to other Target Nucleic Acids

This work was conducted to demonstrate that the present invention is broadly applicable to antisense oligonucleotides ("oligos") specific to nucleic acid targets broadly. The following experimental studies were conducted to show that the method of the invention is broadly suitable for use with anti-sense oligos designed as  $t\epsilon$  ught by this application and targeted to any and all adenosine receptor mRNAs. For this purpose, various anti-sense oligos were porepared to adenosine receptor mRNAs exemplified by the adenosine  $A_1$ ,  $A_{2b}$  and  $A_3$  receptor mRNAs. Anti-sense Oligo I was disclosed above (SEQ. ID NO:1). Five additional anti-sense phosphorothioate oligos were designed asnd synthesized as indicated above.

- 1- Oligo II (SEQ. ID NO: 7) also targeted to the adenosine A, receptor, but to a different region than Oligo I.
- 2- Oligo V (SEQ. ID NO: 10) targeted to the adenosine  $\rm A_{2b}$  receptor.
- 3- Oligos III (SEQ. ID NO: 8) and IV (SEQ. ID NO: 9) targeted to different regions of the adenosine A<sub>3</sub> receptor.
- 4- Oligo I-PD (SEQ. II) NO: 1681)(a phosphodiester oligo of the same sequence as Oligo I).

These anti-sense oligos were designed for therapy on a selected species as described above and are generally specific for that species, unless the segment of the target mRNA of other species happens to contain a similar sequences. All anti-sense oligos were prepared as described below, and tested in vivo in a rabbit model for bronchoconstriction, inflammation and allergy, which have breathing difficulties and impeded lung airways, as is the case in ailments such as asthma, as described in the above-identified application.

### 30 Example 6: Design & Sequences of other Anti-sense Oligos

Six oligos and their effects in a rabbit model were studied and the results of these studies are reported and discussed below. Five of these oligos were selected for this study to complement the data on Oligo I (SEQ ID NO: 1) provided in Examples 1 to 4 above. This oligo is anti-sense to one region of the adenosine A<sub>1</sub> receptor mRNA. The oligos tested are identified as anti-sense Oligos I (SEQ ID NO: 1) and II (SEQ. ID No: 7) targeted to a different region of the adenosine A<sub>1</sub> receptor mRNA, Oligo V (SEQ. ID No:8) targeted to the adenosine A<sub>2b</sub> receptor mRNA, and anti-sense Oligos III and IV (SEQ. ID NOS: 9 and 10) targeted to two different regions of the adenosine A<sub>3</sub> receptor mRNA. The sixth oligo (Oligo I-PD) is a phosphodiester version of Oligo I (SEQ. ID NO:1). The design and synthesis of these anti-sense oligos was performed in accordance with Example 1 above.

#### (I) Anti-sense Oligo I

The anti-sense oligonucleotide I referred to in Examples 1 to 4 above is targeted to the human A<sub>1</sub> adenosine receptor rnRNA (EPI 2010). Anti-sense oligo I is 21 nucleotide long, overlaps the initiation codon, and has the following sequence:5'-GAT GGA GGG CGG CAT GGC GGG-3'(SEQ.ID NO:1). The oligo I was previously shown to abrogate the adenosine-induced bronchoconstriction in allergic rabbits, and to reduce allergen-induced airway obstruction and bronchial hyperresponsiveness (BHR), as discussed above and shown by Nyce, J. W. & Metzger, W. J., Nature, 385:721 (1977), the relevant portions of which reference are incorporated in their entireties herein by reference.

### (II) Anti-sense Oligo II

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A phosphorothioate anti-sense oligo (SEQ. ID NO:7) was designed in accordance with the invention to target the rabbit adenosine A<sub>1</sub> receptor mRNA region +936 to +956 relative to the initiation codon (start site). The anti-sense oligo II is 21 nucleotide long, and has the following sequence: 5'-CTC GTC GCC GTC GCC GGC GGG-3' (SEQ. ID NO:7).

### (III) Anti-sense Oligo III

A phosphotothioate anti-sense oligo other than that provided in Example 1 above (SEQ. ID NO:8) was designed in accordance with the invention to target the anti-sense A<sub>3</sub> receptor mRNA region +3 to + 22 relative to the initiation codon start site. The anti-sense oligo III is 20 nucleotide long, and has the following sequence: 5'-GGG TGC TAT TGT CGG GC-3' (SEQ. ID NO:8).

### 10 (IV) Anti-sense Oligo IV

Yet another phosphorothioate anti-sense oligo (SEQ. ID NO:9) was designed in accordance with the invention to target the adenosine A<sub>3</sub> receptor mRNA region + 386 to + 401 relative to the initiation codon (start site). The anti-sense oligo IV is 15 nucleotide long, and has the following sequence: 5'-GGC CCA GGC CCA GCC-3' (SEQ. ID NO:9)

### 15 (V) Anti-sense Oligo V

A phosphorothioate anti-sense oligo (SEQ. ID NO:10) was designed in accordance with the invention to target the adenosine A<sub>2b</sub> receptor mRNA region -21 to -1 relative to the initiation codon (start site). The anti-sense oligonucleotide V is 21 nucleotide long, and has the following sequence: 5'-GGC CGG GCC AGC CGG GCC CGG-3' (SEQ. ID NO:10).

### (VI) A<sub>1</sub> Mismatch Oligos

Two different mismatched oligonucleotides having the following sequences were used as controls for anti-sense oligo I (SEQ. ID NO: 1) described in Example 5 above: A<sub>1</sub> MM2:5'-GTA GGT GGC GGG CAA GGC GGG-3' (SEQ. ID NO:2421), and A<sub>1</sub> MM3:5'-GAT GGA GGC GGG CAT GGC GGG-3' (SEQ. ID NO:2422). Anti-sense oligo I and the two mismatch anti-sense oligos had identical base content and general sequence structure. Homology searches in GENBANK (release 85.0) and EMBL (release 40.0) indicated that the anti-sense oligo I was specific, not only for the human, but also for the rabbit, adenosine A<sub>1</sub> receptor genes, and that the mismatched controls were not candidates for hybridization with any known human or animal gene sequence.

### (VII) Anti-sense Oligo A<sub>1</sub>-PD (Oligo VI)

A phosphodiester anti-sense oligo (Oligo VI; SEQ. ID NO:2420) having the same nucleotide sequence as Oligo I was designed as disclosed in the above-identified application. Anti-sense oligo I-PD is 21 nucleotide long, overlaps the initiation codon, and has the following sequence: 5'- GAT GGA GGG CGG CAT GGC GGG-3' (SEQ. ID NO:2420).

### III) Controls

Each rabbit was administered 5.0 ml aerosolized sterile saline following the same schedule as for the anti-sense oligos in (II), (III), and (IV) above.

### **Example 7:** Synthesis of Anti-sense Oligos

Phosphorothioate anti-sense oligos having the sequences described in (a) above, were synthesized on an Applied Biosystems Model 396 Oligonucleotide Synthesizer, and purified using NENSORB chromatography (Di Pont, DE). TETD (tetraethylthiuram disulfide) was used as the sulfurizing agent during the synthesis. Anti-sense oligonucleotide II (SEQ. ID NO:7), anti-sense oligonucleotide III (SEQ. ID NO: 8) and anti-sense oligonucleotide IV (SEQ. ID NO: 9) were each synthesized and purified in this manner.

### **Example 8:** Preparation of Allergic Rabbits

Neonatal New Zealand white Pasturella-free rabbits were immunized intraperitoneally within 24 hours of birth with 0.5 ml of 312 antigen units/ml house dust mite (D. *farinae*) extract (Berkeley Biologicals, Berkeley, CA) mixed with 10% kaolin as previously described (Metzger, W. J., in Late Phase Allergic Reactions, Dorsch, W., Ed., CRC Handbook, pp. 347-362, CRC Press, Boca Raton (1990); Ali,

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S., Metzger, W. J. and Mustafa, S. J., Am. J. Resp. Crit. Care Med. 149: 908 (1994)), the relevant portions of which are incorporated in their entireties here by reference. Immunizations were repeated weekly for the first month and then biweekly until the age of 4 months. These rabbits preferentially produce allergen-specific IgE antibody, typically respond to aeroallergen challenge with both an early and late-phase asthmatic response, and show bronchial hyper responsiveness (BHR). Monthly intraperitoneal administration of allergen (312 units dust mite allergen, as above) continues to stimulate and maintain allergen-specific IgE antibody and BHR. At 4 months of age, sensitized rabbits were prepared for aerosol administration as described by Ali et al. (Ali, S., Metzger, W. J. and Mustafa, S. J., Am. J. Resp. Crit. Care Med. 149 (1994)), the relevant section being incorporated in its entirety here by reference.

### 10 DOSE-RESPONSE STUDIES

### **Example 9:** Experimental Setup

Aerosols of either adenosine (0-20 mg/ml), or anti-sense or one of two mismatch oligonucleotides (5 mg/ml) were separately prepared with an ultrasonic nebulizer (Model 646, DeVilbiss, Somerset, PA), which produced aerosol droplets, 80% of which were smaller than 5:m in diameter. Equal volumes of the aerosols were administered directly to the lungs *via* an intratracheal tube. The animals were randomized, and administered aerosolized adenosine. Day 1 pre-treatment values for sensitivity to adenosine were calculated as the dose of adenosine causing a 50% loss of compliance (PC<sub>50</sub> Adenosine). The animals were then administered either the aerosolized anti-sense or one of the mismatch anti-sense oligos via the intratracheal tube (5 mg/1.0 ml), for 2 minutes, twice daily for 2 days (total dose, 20 mg). Post-treatment PC<sub>50</sub> values were recorded (post-treatment challenge) on the morning of the third day. The results of these studies are provided in Example 21 below.

### **Example 10:** Crossover Experiments

For some experiments utilizing anti-sense oligo I (SEQ ID NO: 1) and a corresponding mismatch control oligonucleot de A1MM2, following a 2 week interval, the animals were crossed over, with those previously administered the mismatch control A<sub>1</sub>MM2, now receiving the anti-sense oligo I, and those previously treated with the anti-sense oligo I, now receiving the mismatch control A<sub>1</sub>MM2 oligo. The number of animals rer group was as follows. For mismatch A<sub>1</sub>MM2 (Control 1), n=7, since one animal was lost in the second control arm of the experiment due to technical difficulties, for mismatch A<sub>1</sub>MM3 n=4 (Control 2) and for A<sub>1</sub>AS anti-sense oligo I, n=8. The A<sub>1</sub>MM3 oligo-treated animals were analyzed separately and were not part of the cross-over experiment. The treatment methods and measurements employed following the cross-over were identical to those employed in the first arm of the experiment. In 6 of the 8 animals treated with the anti-sense oligo I (SEQ. ID NO: 1), no PC<sub>50</sub> value could be obtained for adenosine doses of up to 20 mg/ml, which is the limit of solubility of adenosine. Accordingly, the PC<sub>50</sub> values for these an mals were assumed to be 20 mg/ml for calculation purposes. The values given, therefore, represent a minimum figure for the effectiveness of the anti-sense oligonucleotides of the invention. Other groups of allergic rabbits (n=4 for each group) were administered 0.5 or 0.05 mg doses of the anti-sense oligo (SEQ ID NO: 1), or the A<sub>1</sub>MM2 oligo in the manner and according to the schedule described above (the total doses being 2.0 or 0.2 mg). The results of these studies are provided in Example 22 below.

#### 40 Example 11: Ar ti-sense Oligo Formulation

Each one of anti-sense oligos were separately solubilized in an aqueous solution and administered as described for anti-sense oligo I (SEQ. ID No:1) in (e) above, in four 5 mg aliquots (20 mg total dose) by means of a nebulizer via endotracheal tube, as described above. The results obtained for anti-sense oligo I and its mismatch controls confirmed that the mismatch controls are equivalent to saline, as described in Example 19 below and in Table 1 of Nyce & Metzger, Nature 385: 721-725 (1997). Because of this finding, saline was used as a control for pulmonary function studies employing anti-sense oligos II, III and IV (SEQ. IS NOS; 7, 8 and 9).

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### Example 12: Specificity of Oligo I for Adenosine A<sub>1</sub> Receptor (Receptor Binding Studies)

Tissue from airway smooth muscle was dissected to primary, secondary and tertiary bronchi from rabbits which had been administered 20 mg oligo I (SEQ ID NO: 1) in 4 divided doses over a period of 48 hours as described above. A membrane fraction was prepared according to the method of Ali et al. (Ali, S., et al., Am. J. Resp. Crit. Care Med. 149: 908 (1994), the relevant section relating to the preparation of the membrane fraction is incorporated in its entirety hereby by reference). The protein content was determined by the method of Bradford and plasma membranes were incubated with 0.2 U/ml adenosine deaminase for 30 minutes at 37EC to remove endogenous adenosine. See, Bradford, M. M. Anal. Biochem. 72, 240-254 (1976), the relevant portion of which is hereby incorporated in its entirety by reference. The binding of [3H]DPCPX, [3H]NPC17731, or [3H]CGS-21680 was measured as described by Jarvis et al. See, Jarvis, M.F., et al., Pharmacol. Exptl. Ther. 251, 888-893 (1989), the relevant portion of which is fully incorporated herein by reference. The results of this study are shown in Table 8 and discussed in Example 20 below.

### Example 13: Pulmonary Function Measurements (Compliance c<sub>DYN</sub> and Resistance)

At 4 months of age, the immunized animals were anesthetized and relaxed with 1.5 ml of a mixture of ketamine HCl (35 mg/kg) and acepromazine maleate (1.5 mg/kg) administered intramuscularly. After induction of ar esthesia, allergic rabbits were comfortably positioned supine on a soft molded animal board. Salve was applied to the eyes to prevent drying, and they were closed. The animals were then intubated with a 4.0 mm intermediate high-low cuffed Murphy 1 endotracheal tube (Mallinckrodt, Glen Falls, NY), as previously described by Zavala and Rhodes. See, Zavala and Rhodes, Proc. Soc. Exp. Biol. Med. 144: 509-512 (1973), the relevant portion of which is incorporated herein by reference in its entirety. A polyethylene catheter of OD 2.4 mm (Becton Dickinson, Clay Adams, Parsippany NJ) with an attached thin-walled latex balloon was passed into the esophagus and maintained at the same distance (approximately 16 cm) from the mouth throughout the experiment. The endotracheal tube was attached to a heated Fleisch pneumotach (size 00; DEM Medical, Richmond, VA), and the flow (v) measured using a Validyne differential pressure transducer (Model DP-45-16-1927, Validyne Engineering, Northridge, CA), driven by a Gould carrier amplifier (Model 11-4113, Gould Electronics, Cleveland, OH). An esophageal balloon was attached to one side of the Validyne differential pressure transducer, and the other side was attached to the outflow of the endotracheal tube to obtain transpulmonary pressure (P<sub>m</sub>). The flow was integrated to yield a continuous tidal volume, and the measurements of total lung resistance (R<sub>1</sub>) and dynamic compliance (C<sub>dyn</sub>) were made at isovolumetric and zero flow points. The flow, volume and pressure were recorded on an eight channel Gould 2000 W high-frequency recorder and C<sub>dvn</sub> was calculated using the otal volume and the difference in Ptp at zero flow, and . Rt was calculated as the ratio of Ptp and V at miltidal lung volumes. These calculations were made automatically with the Buxco automated pulmonary mechanics respiratory analyzer (Model 6, Buxco Electronics, Sharon, CT), as previously described by Giles et al. See, Giles et al., Arch. Int. Pharmacodyn. Ther. 194: 213-232 (1971), the relevant portion of which describing these calculations is incorporated in toto hereby by reference. The results obtained upon administration of oligo II on allergic rabbits are shown and discussed in Example 26 below.

### **Example 14:** Measurement of Bronchial Hyperresponsiveness (BHR)

Each allergic rabbit was administered histamine by aerosol to determine their baseline hyperresponsiveness Aerosols of either saline or histamine were generated using a DeVilbiss nebulizer (DeVilbiss, Somerset, PA) for 30 seconds and then for 2 minutes at each dose employed. The ultrasonic nebulizer produced aerosol droplets of which 80% were <5 micron in diameter. The histamine aerosol was administered in increasing concentrations (0.156 to 80 mg/ml) and measurements of pulmonary function were made after each dose. The B4R was then determined by calculating the concentration of histamine (mg/ml) required to reduce the  $C_{\rm dyn}$  50% from baseline (PC<sub>50 Histamine</sub>).

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The measurement of cardiac output and other cardiovascular parameters using CardiomaxJ utilizes the principal of thermal dilution in which the change in temperature of the blood exiting the heart after a venous injection of a known volume of cool saline is monitored. A single rapid injection of cool saline was made into the right atrium via cannulation of the right jugular vein, and the corresponding changes in temperature of the mixed injectate and blood in the aortic arch were recorded via cannulation of the carotid artery by a temperature-sensing miniprobe. Twelve hours after the allergic rabbits had been treated with aerosols of oligo I (EPI 2010; SEQ. ID NO: 1) as described in (d) above, the animals were anesthetized with 0.5 ml/kg of 80% Ketamine and 20% Xylazine. This time point coincides with previous data showing efficacy for SEQ. ID NO: 1, as is clearly shown by Nyce & Metzger, (1997), supra, the pertinent disclosure being incorporated in its entirety here by reference. A thermocouple was then inserted into the left carotid artery of each rabbit, and was then advanced 6.5 cm and secured with a silk ligature. The right jugular vein was then cannulated and a length of polyethylene tubing was inserted and secured. A thermodilution curve was then established on a CardiomaxJ II (Columbus Instruments, Ohio) by injecting sterile saline at 20EC to determine the correctness of positioning of the thermocouple probe. After establishing the correctness of the position of the thermocouple, the femoral artery and vein were isolated. The femo al vein was used as a portal for drug injections, and the femoral artery for blood pressure and heart rate measurements. Once constant baseline cardiovascular parameters were established, CardiomaxJ measurements of blood pressure, heart rate, cardiac output, total peripheral resistance, and cardiac contractility were made.

### **Example 16:** Duration of Action of Oligo I (SEQ. ID NO: 1)

Eight allergic rabbits received initially increasing log doses of adenosine by means of a nebulizer via an intra-tracheal tube as described in (f) above, beginning with 0.156 mg/ml until compliance was reduced by 50% (PC<sub>50 Adenosine</sub>) to establish a baseline. Six of the rabbits then received four 5 mg aerosolized doses of (SEQ. ID NO: 1) as described above. Two rabbits received equivalent amounts of saline vehicle as controls. Beginning 18 hours after the last treatment, the PC<sub>50 Adenosine</sub> values were tested again. After this point, the measurements were continued for all animals each day, for up to 10 days. The results of this study are discussed in Example 25 below.

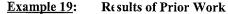
### Example 17: Reduction of Adenosine A<sub>2b</sub> Receptor Number by Anti-sense Oligo V

Sprague Dawley rats were administered 2.0 mg respirable anti-sense oligo V (SEQ ID NO:10) three times over two days using an inhalation chamber as described above. Twelve hours after the last administration, lung parenchymal tissue was dissected and assayed for adenosine  $A_{2b}$  receptor binding using [311]-NECA as described by Nyce & Metzger (1997), supra. Controls were conducted by administration of equal volumes of saline. The results are significant at p<0.05 using Student's paired t test, and are discussed in Example 28 below.

### Example 18: Comparison of Oligo I & Corresponding Phosphodiester Oligo VI (SEQ. ID NO:1681)

Oligo I (SFQ ID NO:1) countered the effects of adenosine and eliminated sensitivity to it for adenosine amounte up to 20 mg adenosine/5.0 ml (the limit of solubility of adenosine). Oligo VI (SEQ ID NO:1681), the phosphodiester version of the oligonucleotide sequence, was completely ineffective when tested in the same manner. Both compounds have identical sequence, differing only in the presence of phosphorothioate residues in Oligo I (SEQ ID NO:1), and were delivered as an aerosol as described above and in Nyce & Metzger (1997), supra. Significantly different at p<0.001, Student's paired t test. The results are discussed in Example 29 below.

### RESULTS OBTAINED FOR ANTI-SENSE OLIGO I (SEQ. ID NO: 1)



The nucleo ide sequence and other data for anti-sense oligo I (SEQ. ID NO: 1), which is specific for the adenosine A receptor, were provided above. The experimental data showing the effectiveness of oligo I in down regulating the receptor number and activity were also provided above. Further information on the characteristics and activities of anti-sense oligo I is provided in Nyce, J. W. and Metzger, W. J., Nature 385:721 (1957), the relevant parts of which relating to the following results are incorporated in their entireties herein by reference. The Nyce & Metzger (1997) publication provided data showing that the antisense oligo I (SEQ. ID NO: 1):

- (1) The anti-sense oligo I reduces the number of adenosine  $A_1$  receptors in the bronchial smooth muscle of allergic rabbits in a dose-dependent manner as may be seen in Table 5 below.
- (2) Anti-sense Oligo I attenuates adenosine-induced bronchoconstriction and allergen-induced bronchoconstriction.
- (3) The Oligo I attenuates bronchial hyperresponsiveness as measured by  $PC_{50}$  histamine, a standard measurement to assess bronchial hyperresponsiveness. This result clearly demonstrates anti-inflammatory activity of the anti-sense oligo I as is shown in Table 5 above.
- (4) As expected, because it was designed to target it, the anti-sense oligo I is totally specific for the adenosine  $A_1$  receptor, and has no effect at all at any dose on either the very closely related adenosine  $A_2$  receptor or the related bradykinin  $B_2$  receptor. This is seen in Table 5 below.
- (5) In contradistinction to the above effects of the Oligo I, the mismatch control molecules MM2 and MM3 (SEQ. ID NO:1682 and SEQ. ID NO:1683) which have identical base composition and molecular weight but differed from the anti-sense oligo I (SEQ ID NO: 1) by 6 and 2 mismatches, respectively. These mismatches, which are the minimum possible while still retaining identical base composition, produced absolutely no effect upon any of the targeted receptors  $(A_1, A_2 \text{ or } B_2)$ .

These results, along with a complete lack of prior art on the use of anti-sense oligonucleotides, such as oligo I, targeted to the adenosine A<sub>1</sub> receptor, are unexpected results. The showings presented in this patent clearly enable and demonstrate the effectiveness, for their intended use, of the claimed agents and method for treating a disease or condition associated with lung airway, such as bronchoconstriction, inflammation, allergi/(ies), and the like.

### **Example 20:** Oligo I Significantly Reduces Response to Adenosine Challenge

The receptor binding experiment is described in Example 12 above, and the results shown in Table 5 below which shows the binding characteristics of the adenosine  $A_1$ -selective ligand [ $_3$ H]DPCPX and the bradykinin  $E_2$ -selective ligand [ $^3$ H]NPC 17731 in membranes isolated from airway smooth muscle of  $A_1$  adenosine receptor and  $B_2$  bradykinin receptor anti-sense- and mismatch-treated allergic rabbits.

Table 5: Binding Characteristics of Three Anti-Sense Oligos

Treatment <sup>1</sup>	A <sub>1</sub> receptor		B <sub>2</sub> receptor	
	Kd	B <sub>max</sub>	Kd	Bmax
Adenosine A <sub>1</sub>	Receptor			
20 mg	0.36±0.029 nM	19±1.52 fmoles*	0.39±0.031 nM	14.8±0.99fmoles
2 mg	0.38±0.030 nM	32±2.56 fmoles*	0.41±0.028 nM	15.5±1.08
0.2 mg	0.37±0.030 nM	49±3.43 fmoles	0.34±0.024 nM	15.0±1.06
$A_1MM1$	(Control)			
20 mg	0.34±0.027 nM	52.0±3.64 fmoles	0.35±0.024 nM	14.0±1.0 fmoles
2 mg	0.37±0.033 nM	51.8±3.88 fmoles	0.38±0.028 nM	14.6±1.02
B <sub>2</sub> A (Bradykinin	Receptor)			
20 mg	0.36±0.028 nM	45.0±3.15 fmoles	0.38±0.027 nM	8.7±0.62

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2 mg	0.39±0.035 nM	44.3±2.90 fmoles	0.34±0.024 nM	11.9±0.76
0.2 mg	$0.40 \pm 0.028 \text{ nM}$	47.0±3.76 fmoles	0.35±0.028 nM	15.1±1.05 fmoles
B <sub>2</sub> MM				
20 mg	0.39±0.031 nM	42.0±2.94 fmoles	0.41±0.029 nM	14.0±0.98 fmoles
2 mg	0.41±0.035 nM	40.0±3.20 fmoles	0.37±0.030 nM	14.8±0.99 fmoles
0.2 mg	0.37±0.029 nM	43.0±3.14 fmoles	0.36±0.025 nM	15.1±1.35 fmoles
Saline Control	0.37±0.041	46.0±5.21	0.39±0.047 nM	14.2±1.35 fmoles

<sup>&</sup>lt;sup>1</sup> Refers to total oli; o administered in four equivalently divided doses over a 48 hour period. Treatments and analyses were performed as described in methods. Significance was determined by repeated-measures analysis of variance (ANOVA), and Tukey=s protected t test. n = 4-6 for all groups.

### **Example 21:** Dose-response Effect of Oligo I

Anti-sense oligo I (SEQ ID NO:1) was found to reduce the effect of adenosine administration to the animal in a dose dependent manner over the dose range tested as shown in Table 6 below.

Table 6:	Table 6: Dose-Response Effect to Anti-sense Oligo I	
<b>Total Dose</b>	PC <sub>50 Adenosine</sub>	
(mg)	(mg Adenosine)	
Anti-sense Oligo I		
0.2	8.32±7.2	
2.0	14.0±7.2	
20	19.5±0.34	
A <sub>1</sub> MM2 oligo (control)		
0.2	2.51±0.46	
2.0	$3.13\pm0.71$	
20	3.25± 0.34	

The above results were studied with the Student's paired t test and found to be statistically different, p=0.05

The oligo I (SEQ. ID NO:1), an anti-adenosine  $A_1$  receptor oligo, acts specifically on the adenosine  $A_1$  receptor, but not on the adenosine  $A_2$  receptors. These results stem from the treatment of rabbits with anti-sense oligo I (SEQ. ID NO.1) or mismatch control oligo (SEQ. ID NO:1682;  $A_1$ MM2) as described in Example 9 above and in Nyce & Metzger (1997), supra (four doses of 5 mg spaced 8 to 12 hours apart via nebu izer via endotracheal tube), bronchial smooth muscle tissue excised and the number of adenosine  $A_1$  and adenosine  $A_2$  receptors determined as reported in Nyce & Metzger (1997), supra.

### Example 22: Specificity of Oligo I (SEQ. ID NO:1) for Target Gene Product

Oligo I (SFQ. ID No:1) is specific for the adenosine A<sub>1</sub> receptor whereas its mismatch controls had no activity. Figure 1 depicts the results obtained from the cross-over experiment described in Example 10 above and in Nyce & Metzger (1997), supra. The two mismatch controls (SEQ. ID NO:1682 and SEQ. ID NO:1683) evidenced no effect on the PC<sub>50 Adenosine</sub> value. On the contrary, the administration of antisense oligo I (SEQ. ID NO:1) showed a seven-fold increase in the PC<sub>50 Adenosine</sub> value. The results clearly indicate that the ant-sense oligo I (SEQ. ID NO: 1) reduces the response (attenuates the sensitivity) to exogenously administered adenosine when compared with a saline control. The results provided in Table 6 above clearly establish that the effect of the anti-sense oligo I is dose dependent (see, column 3 of Table 5). The Oligo I was also shown to be totally specific for the adenosine A<sub>1</sub> receptor, (see, top 3 rows of Table), inducing no activity at either the closely related adenosine A<sub>2</sub> receptor or the bradykinin B<sub>2</sub> receptor (see, lines 8-10 of Table 6 above). In addition, the results shown in Table 6 establish that the anti-sense oligo I (SEQ. ID NO:1) decreases sensitivity to adenosine in a dose dependent manner, and that it does this in an

<sup>\*</sup> Significantly different from mismatch control- and saline-treated groups, p<0.001; \*\*Significantly different from mismatch control- and saline-treated groups, p<0.05.

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anti-sense oligo-der endent manner since neither of two mismatch control oligonucleotides (A<sub>1</sub>MM2; SEQ. ID NO:1682 and A MM3; SEQ. ID NO:1683) show any effect on PC<sub>50 Adenosine</sub> values or on attenuating the number of adenosine A<sub>1</sub> receptors.

### Example 23: E. fect on Aeroallergen-induced Bronchoconstriction & Inflammation

The Oligo I (SEQ. ID NO:1) was shown to significantly reduce the histamine-induced effect in the rabbit model wien compared to the mismatch oligos. The effect of the anti-sense Oligo I (SEQ. ID No:1) and the mis natch oligos (A<sub>1</sub>MM2, SEQ. ID NO:1682 and A<sub>1</sub>MM3, SEQ. ID NO:1682) on allergen-induced airway obstruction and bronchial hyperresponsiveness was assessed in allergic rabbits. The effect of the anti-sense oligo I (SEQ. ID NO:1) on allergen-induced airway obstruction was assessed. As calculated from the area under the plotted curve, the anti-sense oligo I significantly inhibited allergeninduced airway obstruction when compared with the mismatched control (55%, p<0.05; repeated measures ANOVA, and Tukey's t test). A complete lack of effect was induced by the mismatch oligo A<sub>1</sub>MM2 (Control) on allergen induced airway obstruction. The effect of the anti-sense oligo I (SEQ. ID NO:1) on allergen-induced BHR was determined as above. As calculated from the  $PC_{50 \; Histamine}$  value, the anti-sense oligo I (SEQ. ID NO:1) significantly inhibited allergen-induced BHR in allergic rabbits when compared to the mismatched cor.trol (61%, p<0.05; repeated measures ANOVA, Tukey's t test). A complete lack of effect of the A<sub>1</sub>MM mismatch control on allergen-induced BHR was observed. The results indicated that anti-sense oligo I (SEQ. ID NO: 1) is effective to protect against aeroallergen-induced bronchoconstriction (house dust mite). In addition, the anti-sense oligo I (SEQ. ID NO:1) was also found to be a potent inhibitor of dust m te-induced bronchial hyper responsiveness, as shown by its effects upon histamine sensitivity which incicates anti- inflammatory activity for anti-sense oligo I (SEQ. ID NO:1).

### Example 24: Anti-sense Oligo I is Free of Deleterious Side Effects

The Oligo I (SEQ. ID NO:1) was shown to be free of side effects that might be toxic to the recipient. No changes in arterial blood pressure, cardiac output, stroke volume, heart rate, total peripheral resistance or heart contractility (dPdT) were observed following administration of 2.0 or 20 mg oligo I (SEQ. ID NO:1). The addition, the results of the measurement of cardiac output (CO), stroke volume (SV), mean arterial pressure (MAP), heart rate (HR), total peripheral resistance (TPR), and contractility (dPdT) with a CardiomaxJ apparatus (Columbus Instruments, Ohio) were assessed. evidenced that oligo I (SEQ. ID NO:1) has no detrimental effect upon critical cardiovascular parameters. More particularly, this oligo does not cause hypotension. This finding is of particular importance because other phosphorothioate anti-sense oligonucleotides have been shown in the past to induce hypotension in some model systems. Furthermore, the adenosine A1 receptor plays an important role in sinoatrial conduction within the heart. Attenuation of the adenosine A<sub>1</sub> receptor by anti-sense oligo I (SEQ. ID NO:1) might be expected to result, therefore, in deleterious extrapulmonary activity in response to the downregulation of the receptor. This is not the case. The anti-sense oligo I (SEQ. ID NO:1) does not produce any deleterious intrapulmonary effects and renders the administration of the low doses of the present anti-sense oligo free of unexpected, undesirable side effects. This demonstrates that when oligo I (SEQ. ID NO:1) is administered directly to the lung, it does not reach the heart in significant quantities to cause deleterious effects. This is in contrast to traditional adenosine receptor antagonists like theophylline which do escape the lung and can cause deleterious, even life-threatening effects outside the lung.

### **Example 25:** Long Lasting Effect of Oligo I

The Oligo I (SEQ. ID NO:1) evidenced a long lasting effect as evidenced by the  $PC_{50}$  and Resistance values obtained upon its administration prior to adenosine challenge. The duration of the effect was measured for with respect to the  $PC_{50}$  of adenosine anti-sense oligo I when administered in four equal doses of 5 mg each by means of a nebulizer via an endotracheal tube, as described above. The effect of the agent is significant over days 1 to 8 after administration. When the effect of the anti-sense oligo I (SEQ. ID

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NO:1) had disappeared, the animals were administered saline aerosols (controls), and the  $PC_{50}$  Adenosine values for all animals were measured again. Saline-treated animals showed base line  $PC_{50}$  adenosine values (n=6). The duration of the effect (with respect to Resistance) was measured for six allergic rabbits which were administered 20 mg of anti-sense oligo I (SEQ. ID NO: 1) as described above, upon airway resistance measured as also described above. The mean calculated duration of effect was 8.3 days for both  $PC_{50}$  adenosine (p<0.05) and resistance (p<0.05). These results show that anti-sense oligo I (SEQ. ID NO:1) has an extremely long duration of action, which is completely unexpected.

### **Example 26:** A nti-sense Oligo II

Anti-sense oligo II, targeted to a different region of the adenosine  $A_1$  receptor mRNA, was found to be highly active against the adenosine  $A_1$ -mediated effects. The experiment measured the effect of the administration of anti-sense oligo II (SEQ. ID NO:7) upon compliance and resistance values when 20 mg anti-sense oligo II or saline (control) were administered to two groups of allergic rabbits as described above. Compliance and resistance values were measured following an administration of adenosine or saline as described above in Example 13. The effect of the anti-sense oligo of the invention was different from the control in a statistically significant manner, p<0.05 using paired t-test, compliance; p<0.01 for resistance. The results showed that anti-sense oligo II (SEQ. ID NO:7), which targets the adenosine  $A_1$  receptor, effectively maintains compliance and reduces resistance upon adenosine challenge.

### **Example 27:** Antisense Oligos III and IV

Oligos III (SEQ. ID NO:8) and IV (SEQ. ID NO:9) were shown to be in fact specifically targeted to the adenosine A<sub>3</sub> receptor by their effect on reducing inflammation and the number of inflammatory cells present upon separate administration of 20 mg of the anti-sense oligos III (SEQ. ID NO:8) and IV (SEQ. ID NO:9) to allergic rabbits as described above. The number of inflammatory cells was determined in their bronchial lavage fluid 3 hours later by counting at least 100 viable cells per lavage. The effect of anti-sense oligos III (SEQ. ID NO:8) and IV (SEQ. ID NO:9) upon granulocytes, and upon total cells in bronchial lavage were assessed following exposure to dust mite allergen. The results showed that the antisense oligo IV (SEQ. ID NO:9) and anti-sense oligo III (SEQ. ID NO:8) are very potent antiinflammatory agents in the asthmatic lung following exposure to dust mite allergen. As is known in the art, granulocytes, especially eosinophils, are the primary inflammatory cells of asthma, and the administration of an i-sense oligos III (SEQ. ID NO:8) and IV (SEQ. ID NO:9) reduced their numbers by 40% and 66%, respectively. Furthermore, anti-sense oligos IV (SEQ. ID NO:9) and III (SEQ. ID NO:8) also reduced the total number of cells in the bronchial lavage fluid by 40% and 80%, respectively. This is also an important ir dicator of anti-inflammatory activity by the present anti-adenosine A3 agents of the invention. Inflammation is known to underlie bronchial hyperresponsiveness and allergen-induced bronchoconstriction in asthma. Both anti-sense oligonucleotides III (SEQ. ID NO:8) and IV (SEQ. ID NO:9), which are targeted to the adenosine A3 receptor, are representative of an important new class of anti-inflammatory agents which may be designed to specifically target the lung receptors of each species.

### **Example 28:** Ar ti-sense Oligo V

The anti-sense oligo V (SEQ. ID NO:10), targeted to the adenosine  $A_{2b}$  adenosine receptor mRNA was shown to be highly effective at countering adenosine  $A_{2b}$ -mediated effects and at reducing the number of adenosine  $A_{2b}$  receptors present to less than half.

## Example 29: Un expected Superiority of Substituted over Phosphodiester-residue Oligo I-DS (SEQ. ID NO:1681)

Oligos I (SLQ. ID NO:1) and I-DS (SEQ. ID NO:1681) were separately administered to allergic rabbits as described above, and the rabbits were then challenged with adenosine. The phosphodiester oligo I-DS (SEQ. ID NO:1681) was statistically significantly less effective in countering the effect of adenosine whereas oligo I (SEQ. ID NO:1) showed high effectiveness, evidencing a PC<sub>50 Adenosine</sub> of 20 mg.

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### Example 30: Anti-sense Oligo VI

For the present work, I designed an additional anti-sense phosphorothioate oligo targeted to the adenosine A<sub>1</sub> receptor (Oligo VI). This anti-sense oligo was designed for therapy on a selected species as described in the above patent application and is generally specific for that species, unless the segment of the adenosine recep or mRNA of other species elected happens to have a similar sequence. The anti-sense oligos were prepared as described below, and tested in vivo in a rabbit model for bronchoconstriction, inflammation and lung allergy, which have breathing difficulties and impeded lung airways, as is the case in ailments such as asthma, as described in the above-identified application. One additional oligo and its effect in a rabbit model was studied and the results of the study are reported and discussed below. The present oligo (anti-sense oligo VI) was selected for this study to complement the data on SEQ ID NO: 1 (Oligo I), which is anti-sense to the adenosine A1 receptor mRNA provided in the above-identified patent application. This additional oligo is identified as anti-sense Oligo VI, and is targeted to a different region of the adenosine A1 receptor mRNA than Oligo I. The design and synthesis of this anti-sense oligo was performed in accordance with the teaching, particularly Example 1, of the above-identified patent application. The an i-sense Oligo VI is a phosphorothioate designed to target the coding region of the rabbit adenosine A<sub>1</sub> receptor mRNA region +964 to +984 relative to the initiation codon (start site). The Oligo VI was prepared as described in the above-indicated application, and is 20 nucleotides long. The OligoVI is directed to the adenosine A<sub>1</sub> receptor gene, and has the following sequence: 5'-CGC CGG CGG GTG CGG GCC GG-3' (SEQ. ID NO: ). The phosphorothioate anti-sense Oligo VI having the sequence described in (5) above, was synthesized on an Applied Biosystems Model 396 Oligonucleotide Synthesizer, and purified using NENSORB chromatography (DuPont, DE). TETD (tetraethylthiuram disulfide) was used as the sulfurizing agent during the synthesis.

### **Example 31:** Preparation of Allergic Rabbits

Neonatal New Zealand white Pasturella-free rabbits were immunized intraperitoneally within 24 hours of birth with 0.5 ml of 312 antigen units/ml house dust mite (D. farinae) extract (Berkeley Biologicals, Berkeley, CA) mixed with 10% kaolin as previously described (Metzger, W. J., in Late Phase Allergic Reactions, Dorsch, W., Ed., CRC Handbook, pp 347-362, CRC Press, Boca Raton, 1990; Ali, S. Et al., Am. J. Resp. Crit. Care Med. 149: 908 (1994)). The immunizations were repeated weekly for the first month and then bi-weekly until the animals were 4 months old. These rabbits preferentially produce allergen-specific IgE antibody, typically respond to aeroallergen challenge with both an early and late-phase asthmatic response, and show bronchial hyper responsiveness (BHR). Monthly intraperitoneal administration of al ergen (312 units dust mite allergen, as above) continues to stimulate and maintain allergen-specific IgE antibody and BHR. At 4 months of age, sensitized rabbits were prepared for aerosol administration as described by Ali et al. (1994), supra.

### 35 Example 32: Adenosine Aerosol Preparation

An adenos ne aerosol (20 mg/ml) was prepared with an ultrasonic nebulizer (Model 646, DeVilbiss, Somerse, PA), which produced aerosol droplets, 80% of which were smaller than 5:m in diameter. Equal volumes of the aerosols were administered directly to the lungs via an intratracheal tube to all three rabbits. The animals were then administered the aerosolized adenosine and Day 1 pre-treatment values for sensitivity to adenosine were calculated as the dose of adenosine causing a 50% loss of compliance (PC<sub>50</sub> Adenosine). The animals were then administered the aerosolized anti-sense via the intratracheal tube (5 mg/1.0 ml), for 2 minutes, twice daily for 2 days (total dose, 20 mg). Post-treatment PC<sub>50</sub> values were recorded (post-treatment challenge) on the morning of the third day. The results of these studies are provided in (9) below.

### 45 Example 33: Ar ti-sense Oligo Formulation

Each one of anti-sense oligos were separately solubilized in an aqueous solution and administered as described for anti-sense oligo I in (e) above, in four 5 mg aliquots (20 mg total dose) by means of a nebulizer via endotracheal tube, as described above.

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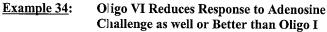
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Oligo VI was tested in three allergic rabbits of the characteristics and readied as described in (7) above and in the above-indicated patent application. Oligo VI targets a section of the coding region of the A<sub>1</sub> receptor which is different from Oligo I. Both these target sequences were selected randomly from many possible coding region target sequences. The three rabbits were treated identically as previously indicated for Oligo I. Briefly, 5 mg of Oligo VI were nebulized to the rabbits twice per day at 8 hour intervals, for two days. Thereafter, PC<sub>50</sub> adenosine studies were performed on the morning of the third day and compared to pre-treatment PC<sub>50</sub> values. This protocol is described in more detail in Nyce and Metzger (Nyce & Metzger, Nature 385: 721-725 (1997)). The results obtained for the three rabbits are shown in Table 7 below.

<u>Table 7</u> :	PC <sub>50</sub> Adenosine before & after	
	Aerosolized Adenosine Treatment	
Treatment Time	PC <sub>50</sub> Adenosine	
	(mg)	
Pre-treatment	$3.0 \pm 2.1$	
Post-treatment	>20.0*	
* ınaximum achievable	dose due to adenosine insolubility in saline	

All three animals treated with Oligo VI completely eliminated sensitivity to adenosine up to the measurable level of the agent shown in Table 7 above. That is, the administration of the Oligo VI abrogated the adenosine-induced bronchoconstriction in the three allergic rabbits. The actual efficacy of Oligo VI is, therefore, greater than could be measured in the experimental system used. By comparing with the previously submitted results for the Oligo I, it may be seen that the Oligo VI was found to be as effective, or more, than Oligo I.

#### 25 Example 34: Conclusions

The work described and results discussed in the examples clearly indicates that all anti-sense oligonucleotides designed in accordance with the teachings of the above-identified application were found to be highly effective at countering or reducing effects mediated by the receptors they are targeted to. That is, each and all of the two anti-sense oligos targeting an adenosine A<sub>1</sub> receptor mRNA, 1 anti-sense oligo targeting an adenosine A<sub>2b</sub> receptor mRNA, and the 2 anti-sense oligos targeting an A<sub>3</sub> receptor mRNA were shown capable of countering the effect of exogenously administered adenosine which is mediated by the specific receptor they are targeted to. The activity of the anti-sense oligos of this invention, moreover, is specific to the target and substitutively fails to inhibit another target. In addition, the results presented also show that the administration of the present agents results in extremely low or non-existent deleterious side effects or toxicity. This represents 100% success in providing agents that are highly effective and specific in the treatment of bronchoconstriction and/or inflammation. This invention is broadly applicable in the same manner to all gene(s) and corresponding mRNAs encoding proteins involved in or associated with airway diseases. A comparison of the phosphodiester and a version of the same oligonucleotide wherein the phosphodiester bonds are substituted with phosphorothioate bonds evidenced an unexpected superiority for the pl osphothiorate oligonucleotide over the phosphodiester anti-sense oligo.

### Example 35: In Vivo Response to Adenosine Challenge with & without Oligo I Pretreatment

Two hyper responsive monkeys (ascaris sensitive) were challenged with inhaled adenosine, with and without pre-treatment with anti-sense oligo I (SEQ.ID NO: 1). The PC<sub>40</sub> adenosine was calculated from the data collected as being equivalent to that amount of adenosine in mg that causes a 40% decrease in dynamic compliance in hyper-responsive airways. The Oligo I (SEQ. ID NO:1; EPI 2010) was subsequently administered at 10 mg/day for 2 days by inhalation. On the third day, the PC adenosine was again measured. The PC<sub>40</sub> adenosine value prior to treatment with Oligo I was compared side-by-side with

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to the PC<sub>40</sub> adenosine taken after administration of Oligo I (Figure not shown). The results of the experiment conduced with two animals showed that any sensitivity to adenosine was completely eliminated by the administration of the oligo of this invention in one animal, and substantially reduced in the second.

### 5 Example 36: Extension of the experimental Results

The method of the present invention is also practiced with anti-sense oligonucleotides targeted to many genes, mRNAs and their corresponding proteins as described above, in essentially the same manner as given above, for the treatment of various conditions in the lungs. Examples of these are Human A2a adenosine receptor, Human A2b adenosine receptor, Human IgE receptor β, Human Fc-epsilon receptor CD23 antigen (IgE receptor), Human IgE receptor, α subunit, Human IgE receptor, Fc epsilon R, Human histidine decarboxylase, Human beta tryptase, Human tryptase-I, Human prostaglandin D synthase, Human cyclooxygenase-2, Human eosinophil cationic protein, Human eosinophil derived neurotoxin, Human eosinophil peroxidase, Human intercellular adhesion molecule-1 (CAM-1), Human vascular cell adhesion molecule 1 (VCAM-1), Human endothelial leukocyte adhesion molecule (ELAM-1), Human P Selectin, Human endothelial monocyte activating factor, Human IL3, Human IL4, Human IL5, Human IL6, Human monocyte-derived neutrophil chemotactic factor, Human neutrophil elastase (medullasin), Human neutrophil oxidase factor, Human cathepsin G, Human defensin 1, Human defensin 3, Human muscarinic acetylcholine receptor HM1, Human muscarinic acetylcholine receptor HM3, Human fibronectin, Human interleukin 8, Human GM-CSF, Human tumor necrosis factor α, Human leukotriene C4 synthase, Human major basic protein, and many more.

The forego ng examples are illustrative of the present invention, and are not to be construed as limiting thereof. The invention is defined by the following claims, with equivalents of the claims to be included therein.

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### WHAT IS CLAIMED AS NOVEL & UNOBVIOUS IN UNITED STATES LETTERS PATENT IS:

1. A pharmaceutical composition, comprising

an oligonucleotide(s) (oligo(s)) which is (are) effective for alleviating bronchoconstriction and/or lung inflammation, allergy(ies), or surfactant depletion or hyposecretion, when administered to a mammal, the oligo containing about 0 to about 15% adenosine (A) and being anti-sense to a target selected from the group consisting of the initiation codon, the coding region, the 5'-end and the 3'-end genomic flanking regions, the 5' and 3' intron-exon junctions, and regions within 2 to 10 nucleotides of the junctions of a gene encoding a target polypeptide associated with lung airway dysfunction or anti-sense to the polypeptide mRNA; combinations of the oligos; and mixtures of the oligos; and

a pharmaceutically or veterinarily acceptable carrier or diluent.

- 2. The composition of claim 1, wherein the oligo is A-free.
- 3. The composition of claim 1, wherein the target is selected from the group consisting of the initiation codon, the coding region, the 5'-end and the 3'-end genomic flanking regions, the 5' and 3' intron-exon junctiors, and regions within 2 to 10 nucleotides of the junctions of an oncogene(s) and a gene(s) encoding a target polypeptide(s) associated with lung airway dysfunction or anti-sense to the oncogene mRNA and the polypeptide mRNA; combinations of the oligos; and mixtures of the oligos; the polypeptides being selected from the group consisting of peptide factors and transmitters, antibodies, cytokines and chemokines, enzymes, binding proteins, adhesion molecules, their receptors, and malignancy associated proteins.
- 4. The composition of claim 3, wherein the target is selected from the group consisting of the initiation codon, the coding region, the 5'-end and the 3'-end genomic flanking regions, the 5' and 3' intron-exon junctiors, and regions within 2 to 10 nucleotides of the junctions of an oncogene(s) and a gene(s) encoding a target polypeptide(s) associated with lung airway dysfunction or anti-sense to the oncogene mRNA and the polypeptide mRNA; combinations of the oligos; and mixtures of the oligos; wherein the polypeptides are selected from the group consisting of transcription factors, stimulating and activating peptide factors, cytokines, cytokine receptors, chemokines, chemokine receptors, adenosine receptors, bradykinin receptors, endogenously produced specific and non-specific enzymes, immunoglobulins and antibodies, antibody receptors, central nervous system (CNS) and peripheral nervous and non-nervous system receptors, CNS and peripheral nervous and non-nervous system peptide transmitters, adhesion molecules, defensins, growth factors, vasoactive peptides and receptors, binding proteins, and malign incy associated proteins.
- 5. The agent of claim 4, wherein the encoded polypeptide(s) is(are) selected from the group consisting of adencsine receptors A1, A2a, A2b and A3, bradykinin receptors B1 and B2, Nf6B 35 Transcription Factor, Interleukin-8 Receptor (IL-8 R), Interleukin 5 Receptor (IL-5 R), Interleukin 4 Receptor (IL-4 R), Interleukin 3 Receptor (IL-3 R), Interleukin-1β (IL-1β), Interleukin 1β Receptor (IL-1 R), Eotaxin, Tryotase, Major Basic Protein, \( \beta 2\)-adrenergic Receptor Kinase, Endothelin Receptor A, Endothelin Receptor B, Preproendothelin, Bradykinin B2 Receptor, IgE High Affinity Receptor, Interleukin 1 (IL-1), Interleukin 1 Receptor (IL-1 R), Interleukin 9 (IL-9), Interleukin-9 Receptor (IL-9 R), 40 Interleukin 11 (IL-1), Interleukin-11 Receptor (IL-11 R), Inducible Nitric Oxide Synthase, Cyclooxygenase-1 (COX 1), Cyclo-oxygenase-2 (COX-2), Intracellular Adhesion Molecule 1 (ICAM-1) Vascular Cellular Adhesion Molecule (VCAM), Rantes, Endothelial Leukocyte Adhesion Molecule (ELAM-1), Monocy e Activating Factor, Neutrophil Chemotactic Factor, Neutrophil Elastase, Defensin 1, 2 and 3, Muscarinic Acetylcholine Receptors, Platelet Activating Factor, Tumor Necrosis Factor α, 5lipoxygenase, Phosphodiesterase IV, Substance P, Substance P Receptor, Histamine Receptor, Chymase. CCR-1 CC Chemokine Receptor, CCR-2 CC Chemokine Receptor, CCR-3 CC Chemokine Receptor, CCR-4 CC Chemoltine Receptor, CCR-5 CC Chemokine Receptor, Prostanoid Receptors, GATA-3 Transcription Factor, Neutrophil Adherence Receptor, MAP Kinase, Interleukin-9 (IL-9), NFAT Transcription Factors, STAT 4, MIP-1α, MCP-2, MCP-3, MCP-4, Cyclophillins, Phospholipase A2, Basic

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Fibroblast Growth Factor, Metalloproteinase, CSBP/p38 MAP Kinase, Tryptose Receptor, PDG2, Interleukin-3 (IL-3), Interleukin-1β (IL-1β), Cyclosporin A-Binding Protein, FK5-Binding Protein, α4β1 Selectin, Fibronectin, α4β7 Selectin, Mad CAM-1, LFA-1 (CD11a/CD18), PECAM-1, LFA-1 Selectin, C3bi, PSGL-1, E-Selectin, P-Selectin, CD-34, L-Selectin, p150,95, Mac-1 (CD11b/CD18), Fucosyl transferase, VLA-4, CD-18/CD11a, CD11b/CD18, ICAM2 and ICAM3, C5a, CCR3 (Eotaxin Receptor), CCR1, CCR2, CCR4, CCR5, LTB-4, AP-1 Transcription Factor, Protein kinase C, Cysteinyl Leukotriene Receptor, Tachychinnen Receptors (tach R), I6B Kinase 1 & 2, STAT 6, c-mas and NF-Interleukin-6 (NF-IL-6).

- 6. The composition of claim 1, wherein one or more As is(are) substituted by a universal base selected from the group consisting of heteroaromatic bases which bind to a thymidine base but have antagonist activity and less than about 0.3 of the adenosine base agonist or antagonist activity at the adenosine  $A_1$ ,  $A_{2a}$ ,  $A_{2b}$  and  $A_3$  receptors.
- 7. The composition of claim 6, wherein the heteroaromatic bases are selected from the group consisting of pyrimidines and purines, which may be substituted by O, halo, NH<sub>2</sub>, SH, SO, SO<sub>2</sub>, SO<sub>3</sub>, COOH and branched and fused primary and secondary amino, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkoxy, alkenoxy, acyl, cycloacyl, arylacyl, alkynoxy, cycloalkoxy, aroyl, arylthio, ar/lsulfoxyl, halocycloalkyl, alkylcycloalkyl, alkenylcycloalkyl, alkynylcycloalkyl, haloaryl, alkynylaryl, arylalkyl, arylalkenyl, arylalkynyl, arylcycloalkyl, which may be further substituted by O, halo, NH<sub>2</sub>, primary, secondary and tertiary amine, SH, SO, SO<sub>2</sub>, SO<sub>3</sub>, cycloalkyl, heterocycloalkyl and heteroaryl.
- 8. The composition of claim 7, wherein the pyrimidines and purines are substituted at a position selected from the group consisting of positions 1, 2, 3, 4, 7, and 8, and the pyrimidines and purines are selected from the group consisting of the ophylline, caffeine, dyphylline, etophylline, acephylline piperazine, bamifylline, enprofylline and xantine having the chemical formula

R<sup>1</sup> N C 3 C N R<sup>3</sup>

wherein  $R^1$  and  $R^2$  are independently H, alkyl, alkenyl or alkynyl and  $R^3$  is H, aryl, dicycloalkyl, dicycloalkenyl, dicycloalkynyl, cycloalkynyl, cycloalkynyl, O-cycloalkynyl, O-cycloalkynyl, O-cycloalkynyl, NH<sub>2</sub>-alkylamino-ketoxyalkyloxy-aryl and mono and dialkylaminoalkyl-N-alkylamino-SO<sub>2</sub> aryl.

- 9. The composition of claim 8, wherein the universal base is selected from the group consisting of 3-nitropyrrole-2'-deoxynucleoside, 5-nitro-indole, 2-deoxyribosyl-(5-nitroindole), 2-deoxyribofuranosyl-|5-nitroindole), 2'-deoxynosine, 2'-deoxynebularine, 6H, 8H-3,4-dihydropyrimido [4,5-c] oxazine-7-one or 2-amino-6-methoxyaminopurine.
- 10. The composition of claim 1, where one or more methylated cytocine(s) (<sup>m</sup>C) is(are) substituted for a C in one or more CpG dinocleotide(s), if present in the oligo(s).
- 11. The composition of claim 1, wherein one or more mononucleotide(s) of the oligo(s) is(are) linked or modified by one or more methylphosphonate, 5'-N-carbamate, phosphotriester, phosphorothioate, phosphorodithioate, boranophosphate, formacetal, thioformacetal, thioether, carbonate, carbamate, sulfate, sulfonate, sulfamate, sulfonamide, sulfone, sulfite, sulfoxide, sulfide, hydroxylamine, methylene(methylmino) (MMI), methoxymethyl (MOM), methoxyethyl (MOE), methyleneoxy (methylimino) (MOMI), 2'-O-methyl, phosphoramidate, C-5 substituted residues, or combinations thereof.
- 12. The composition of claim 11, wherein the mononucleotide residues are linked by phosphorothioate residues.
- 13. The composition of claim 1, wherein the anti-sense oligo comprises about 7 to about 60 mononucleotides.

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- 14. The composition of claim 1, wherein the anti-sense oligo comprises fragments 1, 3, 5, 7 and 8 to 2313 (SEQ. ID NOS: 1 through 2419).
- 15. The composition of claim 1, wherein the anti-sense oligo is operatively linked to, or complexed with, an agent selected from the group consisting of cell internalized or up-taken agents and cell targeting agents.
- 16. The composition of claim 15, wherein the cell internalized or up-taken agent is selected from the group consisting of transferrin, asialoglycoprotein and streptavidin.
- 17. The composition of claim 1, wherein the oligo is operatively linked to a vector that is a prokaryotic or eukaryotic vector.
  - 18. The composition of claim 1, wherein the oligo(s) is(are) hybridized to a ribonucleic acid.
  - 19. A cell, carrying the oligo of claim 1.
- 20. The composition of claim 1, wherein the carrier or diluent is selected from the group consisting of gaseous, liquid, and solid carriers or diluents.
- 21. The composition of claim 20, further comprising an agent selected from the group consisting of other therapeutic agents, surfactants, flavoring and coloring agents, fillers, volatile oils, buffering agents, dispersants, RNA inactivating agents, anti-oxidants, flavoring agents, propellants and preservatives.
- 22. The composition of claim 21, comprising one or more oligo(s), a surfactant, and a carrier or diluent for the oligo and the surfactant.
- 23. The composition of claim 21, wherein the the agent is an RNA inactivating agent which comprises an enzyme, optionally an ribozyme.
- 24. The composition of claim 1, wherein the anti-sense oligo is present in an amount of about 0.01 to about 99.99 w/w of the composition.
  - 25. The composition of claim 1, which is a systemic or topical formulation.
- 26. The formulation of claim 25, selected from the group consisting of oral, intrabuccal, intrapulmonary, rectal, intrauterine, intratunor, intracranial, nasal, intramuscular, subcutaneous, intravascular, intratlecal, inhalable, transdermal, intradermal, intracavitary, implantable, iontophoretic, ocular, vaginal, intraarticular, otical, intravenous, intramuscular, intraglandular, intraorgan, intralymphatic, implantable, slow re ease and enteric coating formulations.
- 27. The formulation of claim 26, which is an oral formulation, wherein the carrier is selected from the group consisting of solid and liquid carriers.
- 28. The oral formulation of claim 27, which is selected from the group consisting of a powder, dragees, tablets, capsules, sprays, aerosols, solutions, suspensions and emulsions, optionally oil-inwater and water-in-cil emulsions.
- 29. The formulation of claim 25, which is a topical formulation, wherein the carrier is selected from the group consisting of creams, gels, ointments, sprays, aerosols, patches, solutions, suspensions and emil lsions.
- 30. The formulation of claim 26, which is an injectable formulation, wherein the carrier is selected from the group consisting of aqueous and alcoholic solutions and suspensions, oily solutions and suspensions and oil- n-water and water-in-oil emulsions.
  - 31. The formulation of claim 26, which is a rectal formulation, optionally a suppository.
- 32. The formulation of claim 26, which is a transdermal formulation, wherein the carrier is selected from the group consisting of aqueous and alcoholic solutions, oily solutions and suspensions and oil-in-water and water-in-oil emulsions.
- 33. The transdermal formulation of claim 32, which is an iontophoretic transdermal formulation, wherein the carrier is selected from the group consisting of aqueous and alcoholic solutions, oily solutions and s ispensions and oil-in-water and water-in-oil emulsions, and wherein the formulation further comprises a transdermal transport promoting agent.
  - 34. The formulation of claim 26, which is provided in an implant, a capsule or a cartridge.

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- 35. The composition of claim 20, wherein the carrier is selected from the group consisting of aqueous and alcoholic solutions and suspensions, oily solutions and suspensions and oil-in-water and water-in-oil emulsions.
  - 36. The formulation of claim 20, wherein the carrier comprises a hydrophobic carrier.
- 37. The formulation of claim 36, wherein the carrier comprises lipid vesicles, optionally liposomes, or particles, optionally microcrystals.
- 38. The formulation of claim 37, wherein the carrier comprises liposomes, and the liposomes comprise the anti-sense oligo.
- The formulation of claim 26, which is a respirable or inhalable formulation, optionally an aerosol.
  - 40. The composition of claim 1, in single or multiple unit form.
  - 41. The composition of claim 1, in bulk.
  - 42. A kit, comprising

a delivery device;

in a separate container(s), the oligo(s) of claim 1; and

instructions for adding a carrier and for use of the kit.

- 43. The kit of claim 42, wherein the formulation is a respirable formulation and the delivery device comprises a nebulizer which delivers single metered doses of the formulation.
- 44. The kit of claim 43, wherein the nebulizer comprises an insufflator and the composition is provided in a piercable or openable capsule or cartridge.
- 45. The kit of claim 44, wherein the delivery device comprises a pressurized inhaler and the composition comprises a suspension, solution or dry formulation of the oligo.
- 46. The kit of claim 45, further comprising, in a separate container, an agent selected from the group consisting of other therapeutic agents, surfactants, anti-oxidants, flavoring agents, fillers, volatile oils, dispersants, antioxidants, propellants, preservatives, buffering agents, RNA inactivating agents, cell-internalized or up-taken agents and coloring agents.
- 47. The kit of claim 46, comprising, in separate containers, one or more oligos, one or more surfactants, and a carrier or diluent, and optionally other therapeutic agents.
- 48. The kit of claim 42, wherein the device is a transdermal delivery device, and the kit further comprises a transdermal delivery agent, a transdermal carrier or diluent, and instructions for preparing a transdermal delivery formulation.
- 49. The kit of claim 42, wherein the device is an iontophoretic delivery device, and the kit further comprises iontophoretic agents and instructions for preparing an iontophoretic formulation.
- 50. An in vivo method of delivering an anti-sense oligonucleotide(s) (oligo(s)) to one or more target polynucleotide(s), comprising administering into the respiratory system of a subject one or more oligo(s) that are anti-sense to the polynucleotide(s), in an amount effective to reach and hybridize to the target polynucleotide(s), and reduce the production or availability, or to increase the degradation, of the target mRNA, or to reduce the amount of the target polypeptide present in the lungs.
- 51. An in vivo method of delivering an anti-sense oligonucleotide (oligo) to a target polynucleotide associated with bronchoconstriction and/or lung inflammation, allergy(ies) and/or surfactant hypoproduction, comprising administering to a subject the composition of claim 1, that comprises an amount of the oligo(s) effective to reach and hybridize to the target polynucleotide(s), and reduce or inhibit the polynucleotide(s)' transcription and/or expression and, thereby, alleviating bronchoconstriction and/or lung inflammation, allergy(ies) and/or surfactant hypoproduction.
- 52. The method of claim 51, wherein the administered composition comprises an amount of the oligo(s) and is administered under conditions effective for alleviating bronchoconstriction and/or lung inflammation, allergy(ies) and/or surfactant depletion or hyposecretion, when administered to a mammal.
- 53. The method of claim 51, wherein the composition is administered into the subject's respiratory system.

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- 54. The method of claim 53, wherein the composition is administered directly into the subject's lung (s).
- 55. The method of claim 51, wherein the administered composition comprises an amount of the oligo(s) and is a liministered under conditions effective to reduce the production or availability, or to increase the degrada ion, of the target mRNA or to reduce the amount of the target polypeptide present in the lungs.
  - 56. The method of claim 51, wherein the agent is administered as a respirable aerosol.
- 57. The method of claim 51, wherein the pulmonary obstruction, and/or bronchoconstriction and/or lung inflammation, allergy(ies) and/or surfactant hypoproduction are associated with a disease or condition selected from the group consisting of pulmonary vasoconstriction, inflammation, allergies, asthma, impeded respiration, respiratory distress syndrome (RDS), pain, cystic fibrosis (CF), allergic rhynitis (AR), pulmonary hypertension, emphysema, chronic obstructive pulmonary disease (COPD), pulmonary transplan ation rejection, pulmonary infections, bronchitis, and cancer.
- 58. The method of claim 57, wherein the disease or condition is associated with an allergy(ies), and the oligo is anti-sense to a target selected from the group consisting of the initiation codon, the coding region, the 5'-end and the 3'-end genomic flanking regions, the 5' and 3' intron-exon junctions, and regions within 2 to 10 nucleotides of the junctions of a gene(s) encoding an immunoglobulin(s) and antibody(ies) and immunoglobulin and antibody receptors or are anti-sense to the immunoglobulin(s) and antibody(ies) and immunoglobulin and antibody receptors mRNA; combinations of the oligo(s); and mixtures of the oligos.
- 59. The method of claim 57, wherein the disease or condition is associated with a malignancy or cancer, and the oligo is anti-sense to a target selected from the group consisting of the initiation codon, the coding region, the 5'-end and the 3'-end genomic flanking regions, the 5' and 3' intronexon junctions, and regions within 2 to 10 nucleotides of the junctions of an oncogene(s) and/or encodes a malignancy associated protein, or is(are) anti-sense to the oncogene or malignancy associated protein mRNA; combinations of the oligo(s); and mixtures of the oligos and the oligo(s) is(are) administered in an amount effective to reduce either the level of the protein mRNA or of the malignancy associated protein, or to reduce the growth of or provide beneficial characteristics to malignant cells.
- 60. The method of claim 51, wherein the composition is administered transdermally or systemically.
- 61. The method of claim 60, wherein the composition is administered orally, intracavitarily, intransally, intravaginally, intrauterally, intraarticularly, transdermally, intrabucally, intravenously, subcutaneously, intramuscularly, intravascularly, intratumorously, intraglandularly, intraocularly, intracranial, into an organ, intravascularly, intrathecally, intralymphatically, intraotically, by implantation, by inhalation, intradermally, intrapulmonarily, intraotically, by slow release, by sustained release and by a purp.
  - 62. The method of claim 51, wherein the subject is a non-human mammal.
  - 63. The method of claim 51, wherein the mammal is a human.
- 64. The method of claim 51, wherein the oligo is administered in amount of about 0.005 to about 150 mg/kg body weight.
  - 65. The method of claim 51, wherein the oligo is obtained by
  - (a) selecting fragments of a target nucleic acid having at least 4 contiguous nucleic acids selected from the group consisting of G and C;
  - (b) obtain ng a first oligonucleotide 4 to 60 nucleotides long which comprises the selected fragment and has a C and G nucleic acid content of up to and including about 15%; and
  - (c) obtaining a second oligonucleotide 4 to 60 nucleotides long comprising a sequence which is anti-sense to the selected fragment, the second oligonucleotide having an A base content of up to and including about 15%.
    - 65. The method of claim 64, wherein the oligo is A-free.

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- 66. The method of claim 51, wherein the target is selected from the group consisting of the initiation codon, the coding region, the 5'-end and the 3'-end genomic flanking regions, the 5' and 3' intronexon junctions, and regions within 2 to 10 nucleotides of the junctions of an oncogene or a gene encoding a target polypeptide associated with lung airway dysfunction or anti-sense to the polypeptide or oncogene mRNA; combinations of the oligo(s); and mixtures of the oligos; wherein the polypeptide isselected from the group consisting of transcription factors, stimulating and activating factors, interleukins, interleukin receptors, chemokines, chemokine receptors, endogenously produced specific and non-specific enzymes, immunoglobulins, a tibody receptors, central nervous system (CNS) and peripheral nervous and non-nervous system receptors, CNS and peripheral nervous and non-nervous system peptide transmitters, adhesion molecules defensines, growth factors, vasoactive peptides, peptide receptors and binding proteins, and malign mcy associated proteins.
- 67. The method of claim 51, wherein one or more As in the oligo(s) is(are) substituted by a universal base selected from the group consisting of heteroaromatic bases which bind to a thymidine base but have less than about 0.3 of the adenosine base agonist or antagonist activity at an adenosine  $A_1$ ,  $A_{2a}$ ,  $A_{2b}$  and  $A_3$  receptors.
- 68. The method of claim 67, wherein the heteroaromatic bases are selected from the group consisting of pyrimidines and purines, which may be substituted by O, halo, NH<sub>2</sub>, SH, SO, SO<sub>2</sub>, SO<sub>3</sub>, COOH and branched and fused primary and secondary amino, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkoxy, alkenoxy, acyl, cycloacyl, arylacyl, alkynoxy, cycloalkoxy, aroyl, arylthio, arylsulfoxyl, halocycloalkyl, alkylcycloalkyl, alkenylcycloalkyl, alkynylcycloalkyl, haloaryl, alkynylaryl, arylalkyl, arylalkenyl, arylalkynyl, arylcycloalkyl, which may be further substituted by O, halo, NH<sub>2</sub>, primary, secondary and tertiary amine, SH, SO, SO<sub>2</sub>, SO<sub>3</sub>, cycloalkyl, heterocycloalkyl and heteroaryl.
- 69. The method of claim 67, wherein the pyrimidines and purines are substituted at positions
  1, 2, 3, 4, 7 and 8 and the pyrimidines and purines are selected from the group consisting of theophylline, caffeine, dyphylline, etophylline, acephylline piperazine, bamifylline, enprofylline and xantine having the chemical formula

- wherein R¹ and R² are independently H, alkyl, alkenyl or alkynyl and R³ is H, aryl, dicycloalkyl, dicycloalkenyl, dicycloalkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, O-cycloalkyl, O-cycloalkynyl, NH₂-alkylamino-ketoxyalkyloxy-aryl and mono and dialkylaminoalkyl-N-alkylamino-SO₂ aryl.
  - 70. The method of claim 69, wherein the universal base is selected from the group consisting of 3-nitropyrole-2'-deoxynucleoside, 5-nitro-indole, 2-deoxyribosyl-(5-nitroindole), 2-deoxyribofuranosyl-(5-nitroindole), 2'-deoxyinosine, 2'-deoxynebularine, 6H, 8H-3,4-dihydropyrimido [4,5-c] oxazine-7-one or 2-amino-6-methoxyaminopurine.
    - 71. The method of claim 51, further comprising substituting a methylated cytocine (mC) for a C in one or more CpG dinucleotide(s), if present in the oligo(s).
  - 72. The method of claim 51, further comprising substituting by, or modifying one or more nucleotide residue(s) of the oligo(s) with, methylphosphonate, phosphotriester, phosphorothioate, phosphorodithioate, phosphorodithioate, phosphorodithioate, phosphorodithioate, phosphorodithioate, phosphorodithioate, phosphorodithioate, phosphorodithioate, carbamate, sulfate, sulfonate, sulfamate, sulfonamide, sulfone, sulfite, sulfoxide, sulfide, hydroxylamine, methylene(methyimino) (MMI), methoxymethyl (MOM), methoxyethyl (MOE), methyleneoxy

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(methylimino) (MOMI), methoxy methyl (MOM), 2'-O-methyl, phosphoramidate, C-5 substituted residues, or combinations thereof.

- 73 The method of claim 51, further comprising operatively linking to, or complexing the oligo(s) with, an agent selected from the group consisting of cell internalized and up-taken agent(s) and cell targeting agents.
- 74. The method of claim 73, wherein the cell internalized or up taken agent is selected from the group consisting of transferrin, asialoglycoprotein, and streptavidin.
- 75. The method of claim 73, wherein the cell targeting agent is a vector, optionally a prokaryotic or eukaryotic vector.
- 76. A nethod of treating a disease or condition associated with a target selected associated with a disease or condition afflicting lung airways, comprising conducting the method of claim 56.
- 77. The method of claim 76, wehrein the amount of oligo(s) administered is (are) effective to reduce the production or availability, or to increase the degradation, of the mRNA, or to reduce the amount of the polypeptide present in the lungs.
- 78. The method of claim 77, wherein the amount of oligo(s) administered is (are) effective to reduce the production or availability, or to increase the degradation, of the mRNA, or to increase the amount of the surfac ant present in the subject's lungs.
  - 79. The composition of claim 4, wherein the oligo(s) is(are) anti-sense to the initiation codon, the coding region, the 5'-end and the 3'-end genomic flanking regions, the 5' and 3' intron-exon junctions, and regions within 2 to 10 nucleotides of the junctions of a gene(s) encoding an adenosine A1, A2a, A2b and\or A3 receptor, or anti-sense to the adenosine A1, A2a, A2b and\or A3 receptor mRNA.
  - 80. The composition of claim 79, wherein all nucleotide linking residues are phosphorothioates.
    - 81. The composition of claim 1, wherein the oligo is a DNA.
    - 82. The composition of claim 1, wherein the oligo is an RNA.
  - 83. The composition of claim 1, wherein the oligo comprises about 7 to up to about 60 mononucleotides.
  - 84. The composition of claim 79, wherein the oligo(s) is selected from the group consisting of fragment(s) SEQ ID NOS: 1, 3, 5, 7, 8, and/or 11 through 2419, optionally wherein at least one mononucleotide residue is substituted or modified by methylphosphonate, phosphotriester, phosphorothioate, phosphorodithioate, boranophosphate, formacetal, thioformacetal, thioether, carbonate, carbamate, sulfate, sulfonate, sulfamate, sulfonamide, sulfone, sulfite, sulfoxide, sulfide, hydroxylamine, methylene(methyimino), (MMI), methoxymethyl (MOM), methoxyethyl (MOE), methyleneoxy (methylimino) (MOMA), methoxy methyl (MOM), 2'-O-methyl, phosphoramidate residues and/or combinations thereof.
  - 85. The method of claim 51, wherein the oligo is administered topically to the airway, respiratory or pulmonary epithelium of the subject.
  - 86. The composition of claim 1, wherein the oligo has a particle size of about 5-10  $\mu m$  or in the range of 10-500  $\mu m$ .
    - 87. The composition of claim 1, further comprising a propellant.
  - 88. The method of claim 50, wherein the oligo has a particle size of about 5-10  $\mu m$  or in the range of 10-500  $\mu m$ .
    - 89. The method of claim 50, further comprising adding to the oligo a propellant.
- 90. The method of claim 51, wherein the oligo has a particle size of about 5-10  $\mu$ m or in the range of 10-500  $\mu$ m.
  - 91. The method of claim 51, further comprising adding to the oligo a propellant.

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# LOW ADENOSINE ANTI-SENSE OLIGONUCLEOTIDE, COMPOSITIONS, KIT & METHOD FOR TREATMENT OF AIRWAY DISORDERS ASSOCIATED WITH BRONCHOCONSTRICTION, LUNG INFLAMMATION, ALLERGY(IES) & SURFACTANT DEPLETION

### ABSTRACT OF THE INVENTION

An in vivo method of selectively delivering a nucleic acid to a target gene or mRNA, comprises the topical administration, e. g. to the respiratory system, of a subject of a therapeutic amount of an oligonucleotide (oligo) that is anti-sense to the initiation codon region, the coding region, the 5' or 3' intron-exon junction; or regions within 2 to 10 nucleotides of the junctions of the gene, or antisense to a mRNA complementary to the gene in an amount effective to reach the target polynucleotide and reducing or inhibiting express on. In addition a method of treating an adenosine mediated effect, comprises topically administering to a subject an anti-sense oligo in an amount effective to treat the respiratory, pulmonary, or airway disease. In order to minimize triggering adenosine receptors by their metabolism, the administered oligos have a low content of or are essentially free of adenosine. A pharmaceutical composition and formulations comprise the oligo anti-sense to an adenosine receptor, genes and mRNAs encoding them, genomic and mRNA flanking regions, intron and exon borders and all regulatory and functionally related segments of the genes and mRNAs encoding the polypeptides, their salts and mixtures. Various formulations contain a requisite carrier, and optionally other additives and biologically active agents. The low adenosine or adenosine free (des-A) agent for practicing the method of the invention may be prepared by selecting a target gene(s), genomic flanking region(s), RNA(s) and/or polypeptide(s) associated with a disease(s) or condition(s) afflicting lung airways, obtaining the sequence of the mRNA(s) corresponding to the target gene(s) and/or genomic flanking region(s), and/or RNAs encoding the target polypeptide(s), selecting at least one segment of the mRNA which may be up to 60% free of thymidine (T) and synthesizing one or more anti-sense oligonucleotide(s) to the mRNA segments which are free of adenosine (A) by substituting a universal base for A when present in the oligonucleotide. The agent may be prepared by selection of target nucleic acid sequences with GC running stretches, which have low T content, and by optionally replacing A in the anti-sense oligonucleotides with a "Universal or alternative base". The agent, composition and formulations are used for prophylactic, preventive and therapeutic treatment of ailments associated with impaired respiration, lung allergy(ies) and/or inflammation and depletion lung surfactant or surfactant hypoproduction, such as pulmonary vasoconstriction, inflammation, allergies, allergic rhynitis, asthma, impeded respiration, lung pain, cystic fibrosis, bronchoconstriction. The present treatment is suitable for administration in combination with other treatments, e.g. before, during and after other treatments, including radiation, chemotherapy, antibody therapy and surgery, among others. Alternatively, the present agent is effectively administered prophylactically or therapeutically by itself for conditions without known therapies or as a substitute for therapies exhibiting undesirable side effects. The treatment of this invention may be administered directly into the respiratory system of a subject so that the agent has direct access to the lungs, or by other effective routes of administration, e. g. topically, transdermally, by implantation, etc., in an amount effective to reduce or inhibit the symptoms of the ailment.

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